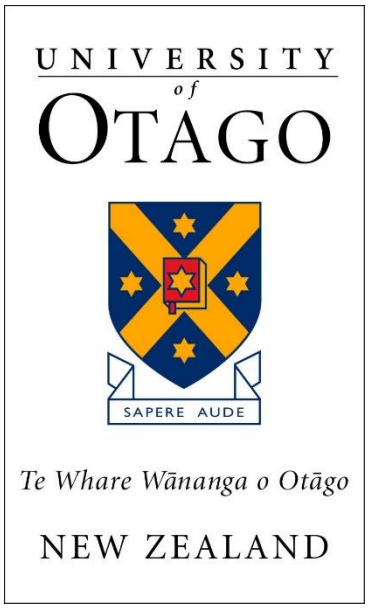
An integrative approach to understanding antimicrobial resistance in New Zealand

Sarah Tariro Mitchell



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Abstract

Antimicrobial resistance (AMR) occurs when micro-organisms (including bacteria, viruses, fungi and parasites) survive exposure to a medicine that would usually kill them or halt their growth. This is a natural phenomenon which is becoming much more common. AMR is a growing public health crisis both globally and in New Zealand. It limits our ability to effectively prevent and treat infectious diseases, and poses a threat to many practices and standards of modern medicine. The rapid development of bacterial resistance to antibiotics is particularly concerning.

AMR is a highly complex issue. There are human, animal and environmental reservoirs of AMR, with complex transmission pathways between them. Their relative importance is unclear and contested. There is increasing recognition of AMR as a 'One Health' issue at the nexus of human, animal and environmental health. Coinciding with this is the recognition that addressing AMR will require new ways of thinking that transcend disciplinary boundaries: we need to think of AMR as a 'system' of interconnecting components, and seek to understand the problem as a whole, and not just its component parts. However, there are few examples of such approaches being applied in practice.

This thesis describes an integrative approach to understanding AMR, which is underpinned by both One Health and EcoHealth principles. EcoHealth is a research paradigm based on the principles of systems thinking, transdisciplinary research, multi-stakeholder participation, sustainability, gender and social equity, and translating knowledge into action. The chosen method, participatory system dynamics, was used to model stakeholder understandings of the causes and effects of AMR in New Zealand, with a particular focus on identifying feedback loops that drive system behaviour over time. Feedbacks are formed by variables connecting into loops that either reinforce or balance changes happening in the system.

This research involved 27 interviews with 31 purposively selected stakeholders who have clinical, academic/research, policy, community and industry experience related to AMR. From the interviews, system dynamics modelling methods were used to build causal loop diagrams representing feedback loops involved in AMR. It is important to learn how

people believe the system works and to integrate the different parts of this complex problem in order to identify key leverage points for improving policy and practice.

Many of the feedback loops arising from this research have not been previously identified in the literature. The results of this research suggest important connections between AMR and other broad issues including poverty, inequality, water quality and intensive farming practices. This is the first time that participatory system dynamics modelling has been used to integrate human, animal and environmental aspects of antimicrobial resistance. It is hoped that future work will refine and strengthen the model through workshops with stakeholders, and develop into simulation of possible policy interventions.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations and Acronyms

AB	Antibiotic
ABR	Antibiotic resistance
AGCARM	New Zealand Association for Animal Health and Crop Protection
AM	Antimicrobial
AMR	Antimicrobial resistance
CLD	Causal loop diagram
ESR	Institute of Environmental Science and Research
FAO	Food and Agricultural Organisation of the United Nations
MRSA	Methicillin-resistant Staphylococcus aureus
NZ	New Zealand
OIE	World Organisation for Animal Health
PHARMAC	Pharmaceutical Management Agency
RTI	Respiratory Tract Infection
SD	System dynamics
pSD	Participatory system dynamics
WHO	World Health Organisation

1 Introduction

1.1 Outline of the problem

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi or parasites survive exposure to drugs that would usually be expected to have killed them. This phenomenon has been recognised since the early 1940s (1), and has grown into a global public health crisis that threatens our ability to effectively treat and prevent infectious diseases (2, 3). According to the World Health Organisation, *"without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill"* (2 p.vii). Infections with resistant organisms limit treatment choices (4) and may require treatment with less desirable antibiotics, which are often more toxic, more expensive and less effective (5). Resistant infections are associated with a higher risk of poor clinical outcomes including longer hospital stays, delayed recovery, disability in the long-term, and increased risk of mortality (6).

There is increasing political recognition of AMR as a major public health issue and acknowledgment that controlling it is essential to long term economic development and global wellbeing (7). The threat of AMR to human health has been likened to that of climate change (8, 9); both are multifactorial, rapidly emerging issues with the potential to become self-sustaining and catastrophic (8). If the increasing trajectory of AMR is not halted, substantial increases in incurable infections are predicted (10, 11). Antibiotics are the most commonly used type of antimicrobial (12), and the general term 'antimicrobial resistance' is commonly used to refer to antibiotic resistance. In this thesis, antimicrobial resistance and antibiotic resistance will be used interchangeably.

AMR is a highly complex issue. A wide range of risk factors have been described across human, animal and environmental systems, but their relative importance is unclear (7). Complexity arises from the fact that *"use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else"* (13 p.78). That is, antibiotic use has implications far beyond the individual or sector using them (14). Antimicrobial drugs are widely used in human and veterinary medicine, and for agricultural purposes (1, 15-17). Although AMR is intrinsically a biological phenomenon, the conditions fostering its growth are social, and shaped by cultural, political and economic factors (18).

Increasingly, researchers and policymakers are realising the importance of understanding AMR as a complex network involving human, animal and environmental health (19), as part of a 'One Health' approach. A One Health approach recognises that human health is intrinsically related to the health of animals and the environment (7), and that multidisciplinary collaboration at a range of scales is necessary to tackle such problems (20).

As well as a One Health approach, this research is underpinned by EcoHealth principles. Both research approaches incorporate holistic, systems-level conceptualisations of human health and its relationship with the health of animals and the environment, recognising the complexity of linkages between these three domains (21-24). The ecosystem approach to health addresses problems that bring together health, equity, and sustainability, using principles of systems thinking, transdisciplinary research, participation, sustainability, gender and social equity, and 'knowledge-to-action' (25). Calls for systems-based approaches to public health are becoming common (26), but so far have been under-used in public health (27, 28). Systems thinking is a way of looking at complex problems that seeks to understand the interconnections between elements of a system in order to achieve a certain purpose (e.g. to reduce AMR) (29).

In order to deal with complexity, integrated approaches to health (such as One Health and EcoHealth) need to be iterative, adaptive and participatory, and participatory modelling provides a practical way for meeting these requirements (30). Participatory modelling purposefully brings affected stakeholders together to facilitate a process of knowledge sharing and model co-generation, to improve planning and decision making in a given context (30). Participatory modelling has been proposed as a useful tool for enabling One Health collaboration between stakeholders in practice (20). Further, it has been recommended for operationalising the principle of systems thinking that is common to both One Health and EcoHealth (30). Participatory modelling is transdisciplinary and facilitates knowledge sharing, knowledge generation, negotiation and planning (30), by allowing integration of various types of information (31). The process of model building helps stakeholders to clarify their own mental models of the problem, appreciate the perspectives of others, and build an enhanced understanding of the system (31).

1.2 Research questions and process

Given the established complexity of AMR and the need for integrated approaches, this project aims to integrate the disparate elements of knowledge about AMR in New Zealand (from human, animal and environmental health dimensions) using One Health and EcoHealth principles. The specific research questions are:

1. *What are the relationships between different aspects of human, animal, and environmental health in relation to antimicrobial resistance, within the New Zealand cultural and political context, as perceived by a variety of stakeholders?*

2. *What are the feedback loops that are driving trends in AMR over time in New Zealand?*

During this research I was guided by a supervisory team with diverse expertise. Alex Macmillan has expertise in EcoHealth approaches and participatory system dynamics modelling. Patricia Priest has expertise in One Health approaches, as well as on the topic of antimicrobial resistance and the stakeholders involved in AMR in New Zealand. Kate Morgaine has expertise in qualitative research approaches. Jeff Foote, a project advisor, also has expertise in systems approaches.

1.3 Structure of this thesis

The structure of the remainder of this thesis is outlined below.

In Chapter Two, I provide further background about AMR and its public health significance. I provide detail about the human, animal and environmental aspects of the problem, and discuss the need for more integrative approaches to tackling AMR.

Chapter Three comprises a literature review on qualitative and quantitative causal models of antimicrobial resistance. Very few models that incorporate human, animal and environmental aspects of AMR were found, and participatory modelling was under-utilised.

Chapter Four describes the underpinning methodological considerations for this research. I describe my personal research approach, One Health and EcoHealth research positions and principles, and introduce systems thinking in more detail. System dynamics is then explained more specifically, and ultimately participatory system dynamics is justified as the research method.

Chapter Five describes the methods used to build a qualitative system dynamics model (causal loop diagram, CLD) of AMR in New Zealand. It details how to read these diagrams, outlines the process of interviewee selection and recruitment, and describes the interviews and the data analysis process (thematic analysis and development of the causal loop diagrams).

In Chapter Six, the first results chapter, I outline the characteristics of the included participants and describe the results of the thematic analysis of interviews.

Chapter Seven, the second results chapter, describes the causal loop diagrams developed in the study and combines them into an overall model.

In Chapter Eight, the final chapter, I discuss the wider meaning of the results, what this study adds to the literature about AMR, evaluate the study and discuss implications for policy, practice and future research. This chapter finishes with some concluding statements.

2 Background

This chapter begins by providing background information about what antimicrobial resistance (AMR) is, how it develops, and its public health significance globally and in New Zealand. The complexity of the problem is illustrated through separate consideration of its human, animal and environmental dimensions. Finally, there is discussion of the importance of a more integrative approach to support understanding and decision making about AMR.

2.1 The burden of infectious diseases

In general, as countries become more developed their infectious disease burden falls and rates of non-communicable diseases rise (32). However, whilst the number of deaths associated with communicable diseases are slowly falling, infectious diseases remain important causes of illness and death, especially in low income countries (32, 33). In 2017, communicable, maternal, neonatal and nutritional causes accounted for 18.6% of deaths worldwide (10.4 million deaths) (33).

Despite New Zealand being a high income country, infectious diseases are still prevalent here and their burden is increasing (34, 35). Between 1989 and 2008, hospitalisations associated with infectious diseases increased in both absolute and relative terms (34). In 1989-93, infectious diseases contributed to 20.5% of acute admissions, and this rose to 26.6% in 2004 - 2008 (34). Infectious diseases are also a source of ethnic and social inequalities in health (34). The young and the elderly, those who are socioeconomically deprived, and Māori and Pacific peoples are disproportionately affected (34, 35). These inequalities in the burden of infectious diseases have increased significantly over the past two decades, especially for Māori and Pacific peoples and those who are in the most socioeconomically deprived quintile (34).

2.2 Antimicrobial resistance

Antimicrobial drugs are medicines that work against infections caused by micro-organisms (36), and include antibiotics, antivirals, antifungals and antiparasitics (14). Antibiotics tend to work by inhibiting the production of proteins or cell wall materials, inhibiting replication of DNA, or disruption of the cell membrane (4). Antimicrobial

resistance occurs when micro-organisms (including bacteria, viruses, fungi and parasites) survive exposure to a medicine that would usually kill them or halt their growth (14, 37, 38). Resistant strains can flourish and spread as susceptible strains are killed (14, 36, 39). The rapid development of bacterial resistance to antibiotics is of particular concern (19, 40), with virtually untreatable bacteria now reported (41, 42).

Antimicrobial resistance is a natural phenomenon (14, 40), but is becoming much more common. Many antimicrobial drugs are naturally produced by fungi or bacteria, and resistance genes have therefore existed in the environment since long before humans started using antibiotics (36, 43, 44). Resistance is a Darwinian selection process that allows microorganisms to survive exposure to many toxic substances (17), and is caused by mutations in microbe genetic material or acquisition of resistance genes from other microbes of the same or different species (45, 46). Alexander Fleming, the discoverer of penicillin, warned about the potential for development of resistance to antibiotics in 1945 (47, 48). Bacteria may acquire a variety of genes that code for different resistance mechanisms, and thus become resistant to multiple antimicrobial agents, which drastically limits options for treatment (45). Historically the progression of AMR was slow and generally manageable by creating new drugs (14), but misuse and overuse of antibiotics has drastically increased the rate of development and spread of resistance (1, 36, 43).

To complicate the situation further, once resistance genes and their genetic vectors have evolved, they may indirectly spread through commensal, environmental, and pathogenic bacteria to reach bacteria anywhere else (13). Resistance genes can be incorporated by an individual's natural microbiota and later be transferred to infecting pathogens (14). Resistance mechanisms can sometimes result in resistance to agents from many classes (cross resistance), or genes encoding resistance mechanisms may be transferred together (co-resistance) (4).

2.3 Public health significance of antimicrobial resistance

AMR is one of the greatest global threats to health in modern times (40, 49), with serious implications for modern medicine as a whole (7, 42, 50). As well as threatening our ability to prevent and treat infectious diseases (5, 40), AMR also threatens many fields

of modern medicine that require effective antibiotics, including surgery, dialysis, neonatal intensive care, and immunosuppressive therapies (5, 36, 40, 42, 49, 51, 52). It is estimated that at least 700,000 people die every year from resistant infections worldwide (38). Multi-drug resistant infections cause an estimated 25,000 deaths in the European Union every year, with associated health care costs and productivity losses of at least 1.5 billion euros (4).

The Review on Antimicrobial Resistance (commissioned by the UK prime minister in 2014, often referred to as the O'Neill Report) predicts that in the absence of urgent action, AMR will result in at least ten million deaths a year by 2050 (more than the projected burden of cancer), with an estimated global cost of up to 100 trillion USD (36). Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) and carbapenemase-producing Enterobacteriaceae (CPE) are key bacterial threats (50). The 2017 Global Burden of Disease Study noted rapid increases in death rates between 2007 and 2017 associated with extensively drug resistant tuberculosis, cellulitis, and *C. Difficile* diarrhoea, citing antibiotic use and resistance as a likely major factor (33).

Bacterial resistance to antibiotics for a range of common diseases is becoming a significant threat to health in New Zealand (42, 53, 54). Resistance to major antibiotic classes including penicillins, fluoroquinolones and third-generation cephalosporins is now widespread in New Zealand hospitals, and is also increasing in the community (49). Community-associated MRSA, bacteria producing ESBL (e.g. *E.coli and Klebsiella pneumonia)* and multi-resistant *Neisseria gonorrhoeae* are all increasing in New Zealand (42). There is some evidence of ethnic inequities in the prevalence of AMR among those with infections, with AMR being higher among Māori and Pacific peoples (55). Antimicrobial use and overuse is said to be the primary contributor to the threat of AMR in New Zealand, and has been increasing in New Zealand in recent years (42). Total antibiotic consumption increased by 49% between 2006 and 2014 (52). Antimicrobial use has been shown to be higher among people who live in more deprived areas (56) and to vary by other characteristics such as age, gender, rurality and ethnicity (57). In 2013,

antibiotic consumption in New Zealand was greater than 22 of 29 European countries that had surveillance data available (52).

2.4 The complexity of antimicrobial resistance

The main risk factor for development and acceleration of AMR is the overuse and inappropriate use of antibiotics (5 p.11), with data showing a direct correlation between antibiotic use and resistance (58). Higher resistance rates are observed in countries with high levels of antibiotic use (59). However, the emergence and spread of resistance is highly complex and there are many gaps in our knowledge (15). There are human, animal and environmental reservoirs of AMR, with complex transmission pathways between them (60). Major risk factors for the emergence and spread of AMR include antimicrobial use in humans and animals, environmental contamination, poor infection prevention and control practices, and poor sanitation, alongside globalisation that facilitates the spread of infections (11, 45).

2.4.1 The absence of new antibiotics

Rapid development of resistance is now combined with a situation of few new antibiotics on the market (61). From 1940-1990, emerging resistance was managed by discovery of new antibiotics (62, 63). However, there are now limited numbers of new antibiotics in the pharmaceutical development 'pipeline' (1, 4, 47, 58), and it is clear that we cannot rely solely on the development of new antimicrobials to address AMR (14). The slowing of antibiotic development has been attributed to scientific challenges in antibiotic discovery (14, 62), licensing issues (62), increased regulatory requirements (63) and decreasing investment in antibiotic research and development (64, 65). Major pharmaceutical companies may be reducing investment due to the limited profitability of antimicrobials, particularly compared with development of drugs for chronic medical conditions (63, 64, 66). The impact of resistance on current and future antibiotic sales as well as the current questioning of the utility of antibiotics for many conditions for which they were previously widely prescribed all contribute to this limited return on investment (63, 66). For pharmaceutical companies, antibiotic development is a situation of high cost and low returns (36).

2.4.2 Antibiotics and AMR in human health

Antibiotics comprise some of the most commonly prescribed medicines in human health, but up to 50% of this may be unnecessary or sub-optimal prescribing (5). A perception of antibiotics as 'wonder drugs' is problematic (40). Inappropriate prescribing has been associated with rising rates of antibiotic resistance (44, 67), with much of this occurring in primary care (59, 68). Antibiotics are overused for many conditions, particularly for respiratory tract infections, which are often viral in origin (58). Physician-related factors, patient-related factors and healthcare system factors may all influence prescribing (67). Patient understanding and education about antimicrobials, as well as behaviours such as not completing recommended treatments and stockpiling antimicrobials, may all contribute to AMR (68). Antibiotic resistance can be a particular problem in countries where antimicrobials are available without prescription or where generally poor sanitation results in increased transmission of infection (1, 44).

Prescribing behaviour has been found to be influenced by a number of factors, including physician experience, knowledge about AMR, diagnostic uncertainty, time pressure, and fear of losing clients if the patient's expectations of getting a prescription are not fulfilled (67). For example, a study found that whilst doctors knew antibiotic prescriptions tend to be of limited usefulness for sore throats, antibiotics were often prescribed to build and preserve relationships (69). In other studies, doctors' perceptions of patient expectations of antibiotics were strong predictors of the decision to prescribe (68, 70, 71). However, studies have also found that this perception of patient expectations can often be incorrect (58, 69). Communication between physicians and patients could be key for bridging gaps in expectations (58).

2.4.3 AMR in food animals – a threat to human health?

The AMR crisis in human medicine has resulted in urgent questioning about the various other uses of antimicrobial drugs, including their use in food and companion animals (8, 61, 65). Many classes of antimicrobials used in animals (both food and companion) are also used for human medicine (12). Antibiotics are widely used in food animals for the purposes of disease prevention, control, and treatment, and for growth-promotion or feed-efficiency (5, 72, 73). In some countries the volume of antibiotics used in food animals is greater than human use (73). Rising demand for animal protein drives intensive

farming of food animals (large groups and high densities), which favours animal production practices associated with the use of large quantities of antibiotics (14, 65). This may increase selection pressure on bacteria, facilitating the emergence of resistance (8, 73, 74). Entire herds or flocks of animals are often treated with antibiotics, in contrast to humans usually being treated as individuals, which adds another level of complexity (14). An estimated 63,151 tonnes of antibiotics were used for animal agriculture worldwide in 2010, and this is predicted to rise by almost 70% by 2030 (73).

There is significant debate about whether antibiotic use in food animals results in resistant infections in humans (46, 61, 72). Numerous possible transmission pathways have been suggested, including that gut bacteria in food producing animals may contaminate meat during slaughter or enter the environment in animal waste, with possible contamination of soil, water and crops (75). The severity and relative impact of risk to human health has not been well characterised (65), possibly in part because *"given divergent stakeholder interests and inadequate research to date, public policy discussions of this issue are often contentious and highly polarized"* (65 p.5). However, there is widespread recognition (including by international organisations such as the World Health Organisation, the Food and Agricultural Organisation of the United Nations (FAO), and the World Organisation for Animal Health (OIE)) that antimicrobial use in food animals poses a risk to human health, and should be approached more judiciously (15, 16, 36, 72, 74, 76).

Use of antibiotics for enhancing production is seen as especially problematic (14, 16), with particular risk attributed to their continuous, low-dose non-therapeutic applications such as growth promotion and disease prevention (5, 9, 16, 47, 72, 77). The regulation of antimicrobial use in food animals varies worldwide (77). The most stringent guidelines ban the use of antibiotics for growth promotion, and require veterinary prescription for antibiotic use (e.g. in the E.U.) (77). Antimicrobial use in food animals in Denmark has reduced by 54% as a result of banning antibiotic growth promoters (74).

A recent review found compelling evidence to support each step in the causal pathway from antimicrobial use in animal agriculture to resistant infections in humans (15). Other authors agree there is growing evidence that the resistant infections in humans can

originate in food-producing animals (75, 78). On the other hand, some question the completeness of the evidence (46, 79). Some authors discuss how banning antimicrobial growth promoters has led to reductions in resistant bacteria prevalence in food, food animals and humans (74), whilst others say such bans have had limited success and can result in worse animal health, and a paradoxical increase in human illness and resistance rates (61, 80). Rising use of antimicrobials in aquaculture is also a concern, being a potential source of contamination of the aquatic environment (72, 73).

2.4.4 Companion animals and AMR

More attention is beginning to be focused on antimicrobial use and bacterial resistance in companion animals (8, 81). Companion animals have uniquely close contact with humans (81), and they may share resistant bacteria, amplify resistant bacteria they acquire from people, or act as a reservoir for human infection (8). Current knowledge of magnitude of these health risks is limited (81). The use of antimicrobial drugs in companion animals is less regulated compared to food animals (8). Much less attention has focused on the impact of AMR acquired by humans from companion animals compared with food animals, and thus may be considerably underestimated (8). However, the emergence of MRSA in companion animals has increased interest in their role in the AMR system (8).

2.4.5 The environmental dimension of AMR

The environment is also an important reservoir of resistance genes including naturally occurring resistance, resistance present in human and animal waste, and resistance resulting from co-selection by pollutants (10). The environment has historically been an under-recognised dimension of AMR (60). Here I define the environment as including inanimate aspects of the natural and built environment, as well as plants and wildlife, which are often considered part of the wider 'ecology'. Antimicrobials can persist largely unchanged for some time in the natural environment (1). Antibiotics excreted by humans or animals that enter the environment can exert selection pressure below therapeutic concentrations, which is ideal for selecting for resistance (44). Antibiotic manufacturing plants can be another important contributor to AMR in the environment, especially in areas where there is high volume production with little environmental regulation (10).

Antibiotics are used in relatively small amounts for disease prophylaxis in horticulture (82) and may also contaminate animal manure that is used as fertiliser for crops (83). Humans may be exposed to antibiotics, resistance genes or resistant bacteria present in the environment through a variety of routes, including: crops exposed to contaminated sludge, manure and slurry; infected livestock products; contaminated fish; contaminated drinking water with pharmaceutical residues; and contaminated coastal waters (10). Wildlife (often considered part of the environment) can also be reservoirs of AMR (60).

Resistance is made more complex by the phenomenon of co-selection. Co-selection occurs when a resistance determinant is associated with other kinds of adaptations, such as resistance to heavy metals (84). For example, environmental contamination by heavy metals such as copper can directly select for heavy metal resistance and, at the same time, indirectly for antibiotic resistance (46). Antibacterials present in many household products can also enter the environment and exert selection pressure, altering the wider microbial ecology (44). Figure 2.1 from Wellington *et al.* (2013) summarises some of the key environmental reservoirs of AMR and their connections with humans and animals.

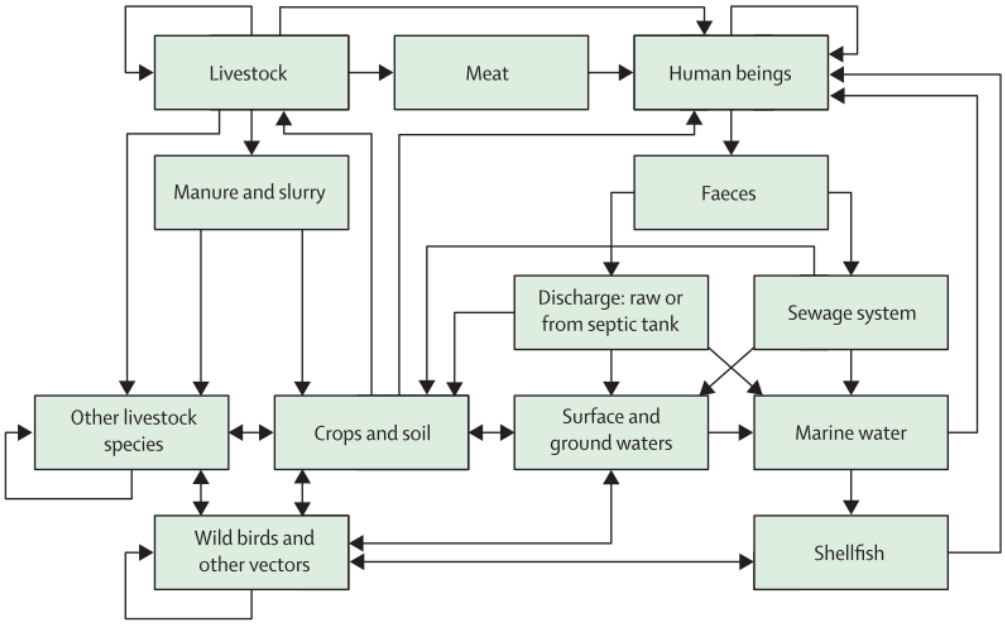

Figure 2.1 Environmental reservoirs of resistance genes: the associations between potential sources of antibiotic resistant bacteria (Wellington et al., 2013)[1]

[1] Reprinted from The Lancet Infectious Diseases, Volume 13, Wellington *et al.*, 'The role of the natural environment in the emergence of antibiotic resistance in gram-negative bacteria', p. 155-165, Copyright 2013, with permission from Elsevier.

2.4.6 Antimicrobial use in human and animal health in New Zealand

In 2013, total antibiotic consumption in human health care in New Zealand was greater than 22 of the 29 European countries with antibiotic consumption data available (52). Antimicrobial use for food animals is less prevalent in New Zealand than other countries, but the authors cautioned that use in this sector could still be further refined. When compared with 26 European countries, Australia, Canada and the United States of America in 2012, New Zealand's use of antimicrobials in animal production was third lowest (an estimated 9.4 mg active ingredient/kg biomass) (11). Use of antimicrobials in humans was 12.9 times the use in animals in New Zealand (11).

2.5 The need for an integrated approach to AMR

It is clear from the above discussion that AMR is a highly complex issue with human, animal and environment dimensions. However, despite AMR being called "*the quintessential One Health problem*" (7), the relative contribution of the three domains in the creation and perpetuation of the AMR problem is poorly understood (7). Although there is acknowledgement that the prevalence of AMR is determined by a complex network of factors, most research currently focuses on one or two parts of the network. Quantifying the relative contribution of each sector to the problem of AMR is difficult (15, 46, 61). Lack of data feeds this ongoing debate regarding which sector contributes the most to the acceleration of AMR, and slows the response of each in taking action (14). In addition, a better understanding of the political and economic context is needed for effective policy-making – this is just as important as the scientific evidence base (85). This wider understanding is lacking in much AMR research and strategy.

There are increasing calls for integrated systems approaches to address antimicrobial resistance (86-89), because it is in these connections and relationships that important keys to the problem may be found. There is also recognised need for models that show the complexity and dynamics of inter-relationships between elements of the wider system (86-89). Models of AMR have often been centred on one domain (e.g. the hospital setting) and usually focused on a small number of proximate factors, rather than taking a broader approach to identifying systemic drivers of the problem (90).

2.6 Summary

In summary, antimicrobial resistance is an important and growing public health threat, with inequitable distribution in New Zealand and globally. Human, animal and environmental settings are all involved in the problem, but there is debate about their relative importance, which slows effective action on AMR. There is increasing recognition of the need for research and policy approaches that integrate these dimensions of AMR (such as One Health approaches) in a systematic way. In the next chapter I describe a literature review of existing research that responds to the above calls for complex modelling of AMR.

3 Literature review of AMR causal models

As established in the background chapter, there is a need for integrated systems approaches to address antimicrobial resistance (86-89). Important solutions to the problem may be found by exploring the connections between variables in a system. Systems approaches often involve the creation of a model, which is a simplified representation of complex processes, to improve understanding (91). The aim of this literature review was to identify previous research that has modelled the AMR system, integrating human, animal and environmental dimensions of AMR in a way that represents a high-level *causal theory* about the problem.

A systematic, comprehensive search strategy and inclusion/exclusion criteria were used to establish the extent of the literature describing causal models of AMR that involve elements from two or three of: human, animal and environment settings. Given the One Health and EcoHealth underpinnings of this research, the focus was on identifying models that integrate human, animal and/or environment disciplines rather than those that only incorporate a single domain. Models intended for influencing policy decisions were of particular interest. Further aims were to identify what modelling techniques have been used, what questions have been asked, and where the knowledge gaps are, as well as to critically assess the quality of included studies.

As identified in the background chapter, models of AMR have often been centred on one domain (e.g. the hospital setting) and usually focused on a small number of proximate factors, rather than taking a broader approach to identifying systemic drivers of the problem (90). Examples include modelling of bacterial population dynamics and the emergence of multidrug resistance (39, 92), and the emergence and/or spread of resistant bacteria in a community/population (93, 94). There are many correlational modelling studies about AMR, for example comparing genetic markers of resistance between animal and human populations (95, 96).

Mathematical modelling approaches have been used to further understanding and support public health decision-making relating about the emergence and spread of resistant strains. However, these mainly focus on microbiological and epidemiological

perspectives, presenting a biological view of the problem (97). Such models have been used to explore the relationships between antibiotic exposure and resistance development, and concepts of antibiotic tolerance and microbial fitness (97) and to model dynamics of person-to-person agent transmission (98).

While the types of models described above can provide useful insights, it is also important to create models that show the complexity and dynamics of inter-relationships between elements of the wider system, as part of an integrated systems approach, to support effective policy-making (86-89). This review aimed to identify such studies.

3.1 Review Methods

3.1.1 Search strategy and study selection

Using a purposive search strategy, I searched Web of Science and Scopus databases using the following search terms:

((*"participatory model*"* OR *"participatory epidemiology"* OR *stakeholder*) OR
(*"systems thinking"* OR *"systems approach"* OR *"system dynamics"* OR *"systems mapping"* OR *"complex system"* OR *"dynamic complexity" OR "system model*" OR "dynamic model")*) OR
(*"one health"* OR *onehealth*) OR
(*ecohealth* OR *"eco health"* OR *"ecosystem approach*"* OR *"ecosystem health"*))
AND
(*"antimicrobial resistance"* OR *"antibiotic resistance"*)

One Health and EcoHealth terms were used in the search as they are increasingly used integrative research approaches, with a focus on systems-level thinking and integration of human, animal and environmental health (23, 99). The initial intention was to search for synonyms of the EcoHealth principles (explained in detail in section 4.2.2) and AMR, however this process returned over 64,000 results. Eventually terms related to transdisciplinary, justice and sustainability were excluded as they did not return relevant results for this search. Systems thinking and modelling phrases and synonyms were included, as well as EcoHealth and One Health synonyms. 'Integrative' search terms were also checked and did not return many relevant results, and those results that were

relevant had been found by the previous search terms. ‘One Health’ was used as a proxy for human, animal and environmental health combined, as it was found that searching for ‘human AND animal AND environment’ was too broad to be useful. The search strategy was also validated by ensuring that the four existing papers I was aware of through background reading and supervisory recommendations were all included in the search results.

Web of Science and Scopus were chosen as the most relevant databases for the research area and question due to their interdisciplinary nature, and following testing of various databases for relevancy of results, and consultation with a librarian. A small number of papers were recommended by supervisors of the project or had been found during previous background research. Grey literature searching included a search of the System Dynamics Review conference proceedings to check for modelling papers about AMR that may not have been published in a journal. This involved searching for “antibiotic resistance” or “antimicrobial resistance” within all available paper lists. All records were managed in Endnote X8.

All retrieved results were screened by title, and papers that clearly did not relate to the research question were excluded. The remaining articles were assessed by screening their abstracts. If there was any uncertainty about how relevant the papers might be, they were retained for further assessment of the full text. The remaining articles were assessed for eligibility by reading the full text. The reference lists of included papers were also screened for further relevant articles.

3.1.2 Criteria for inclusion of studies

To be included in the review, studies had to be specifically or mostly about antimicrobial resistance/antibiotic resistance. They had to include a causal-descriptive model (defined below) of the AMR system that integrates two or more of human, animal and environmental aspects of the problem, with an illustrative diagram. Papers had to be written in English, as translation costs were not feasible for this thesis. Results were not limited by date.

Studies were excluded if they did not model AMR or if the model was not a causal theory. Studies that modelled the AMR system in one setting only or at a micro-level (e.g. bacterial population dynamics/transmission of AMR in a hospital ward/epidemic models) were also excluded. For this review the aim was to find studies that model AMR as an entire system, especially including social, political and economic aspects (here called 'high-level drivers'). Therefore, mechanistic models of biological processes of resistance selection and transmission were excluded. These represent more detailed, micro-level models rather than broader systemic drivers that might assist policy-makers in the face of complexity. Mathematical correlational models were also excluded from detailed analysis as they do not meet the causal theory criteria.

For the purposes of this review, a model is defined as *"a representation or a construction of a reality"* (100 p.450). Barlas (1996) distinguishes between 'causal-descriptive' models which are theory-like models, and models that are purely 'correlational' (data-driven). Causal-descriptive models provide claims about causality through their structure, which can be openly interrogated ('white box'). In contrast, purely correlational models focus on the aggregate output of the model, while the structure may be obscure ('black box'). Correlational models are mainly used for forecasting purposes (e.g. time-series and regression models), while causal-descriptive models are theories about the operation of a system. For causal-descriptive models, the internal structure of the model is crucial to validity (101). As well as reproducing and predicting the behaviour of a system, the model must also be able to explain how the behaviour is generated, and perhaps suggest ways of changing this (101). To be included in this review, models had to specify causal relationships between variables in a model of AMR.

3.1.3 Data extraction and assessment of quality and validity

For each of the full text articles assessed, notes were made in a standardised template (Appendix A) about their background, methods, results, discussion, and further references to look at. A comment about their overall relevance to the literature review was made, as well as which of human/animal/environment dimensions were included, the model type, and whether the model was policy-oriented.

For those studies that met the inclusion criteria for this review, I assess whether the quality and validity of the models has been reported on. Criteria for assessing the quality of causal models are sparse and authors may not report on quality criteria in their published papers. However, Schwaninger and Grösser (2008) build on previous work to present ten criteria for assessing the quality of a model-based theory: refutability, importance, precision and clarity, parsimony and simplicity, comprehensiveness, operationality, validity, reliability, fruitfulness and practicality (100). Coyle (1996) provides a similar set of criteria: clarity and usefulness of purpose, suitability, basis, credibility, creativity, simplicity, redundancy, transparency, flexibility, generality, sensitivity, soundness, productivity and promotion (102). Whilst there is overlap in the quality criteria from different sources, there appears to be no standardised method of assessing the quality of models.

Of the aforementioned quality criteria, very little detail is provided on their meaning and assessment. Detail on assessing the validity of models is most common, therefore validity was the main focus of quality assessment in this review. Even so, validity is rarely discussed (101). It has most often been considered in system dynamics (SD) modelling. Since I was unable to find an article that includes general criteria for assessing the validity of causal-descriptive models, principles of validity that relate to system dynamics models were applied. There are some articles available on assessing the validity of this type of causal model, and the majority of the articles found in the literature review that were most relevant to my research question used system dynamics modelling. In contrast to the relative simplicity of assessing correlational models, assessing the validity of causal-descriptive models can be complicated for both technical and philosophical reasons (see Barlas, 1996 for more).

The validity of a model is how accurately it represents the system under study (100). Model validation has both semi-formal and subjective components (101). For causal-descriptive models (a theory about a real system), questioning the validity of the internal structure of the model is crucial – it must accurately explain how the behaviour of the system is generated (101). In the context of system dynamics modelling, Forrester and Senge (1980) define validation as *"the process of establishing confidence in the soundness and usefulness of a model"* (p.6). It is an iterative process of building

confidence in the model (100, 103, 104), and involves addressing questions of model usefulness in relation to purpose, and structural validity (101, 105, 106).

A model builder uses validation processes to build confidence that the model behaves plausibly (106). Confidence about its usefulness is built as the model withstands attempts to disprove it (106, 107). In order for a model to be useful in enhancing understanding of a problem and contributing to more effective policies, there must be a communication process with a target audience that transfers confidence in the model to those not directly involved in constructing it (106). Usefulness can be assessed by questioning both the modelling process and outcomes of the model's use (108).

Assessing internal validity involves iterative tests of model structure and behaviour (103), of which structural validity is most important to establish first (101, 109). Each detail of the model structure must be examined to judge the merit of the included variables and how well they have been connected (103). Behaviour accuracy - how well the model reproduces the major behaviours shown in the real system (101) - can be tested following satisfaction that the structure of the model is adequate.

For each of the included studies, in the results section of this review I comment on whether the authors discussed how the model was built, whether authors reported assessments of quality and validity, and whether any formal validation procedures (tests of model structure and behaviour) were carried out. I also make an assessment of the model's usefulness in relation to purpose. In some cases, lack of information about these aspects prevents comprehensive comments.

3.1.4 Synthesis of data

For those studies that met the inclusion criteria, I tabulated information about modelling methods used, number of domains (human/animal/environment) covered, process for building the model, and purpose of the model (Table 3.1). The validity of each is discussed.

3.2 Review results

See Figure 3.1 for a flow diagram of the search process and results, based on the preferred reporting items for system reviews and meta-analyses (PRISMA) (110). Most of the records identified through the search were found in Web of Science (360 articles) and Scopus (520 articles) databases. No relevant papers were found among the reference lists of the included papers (392 references).

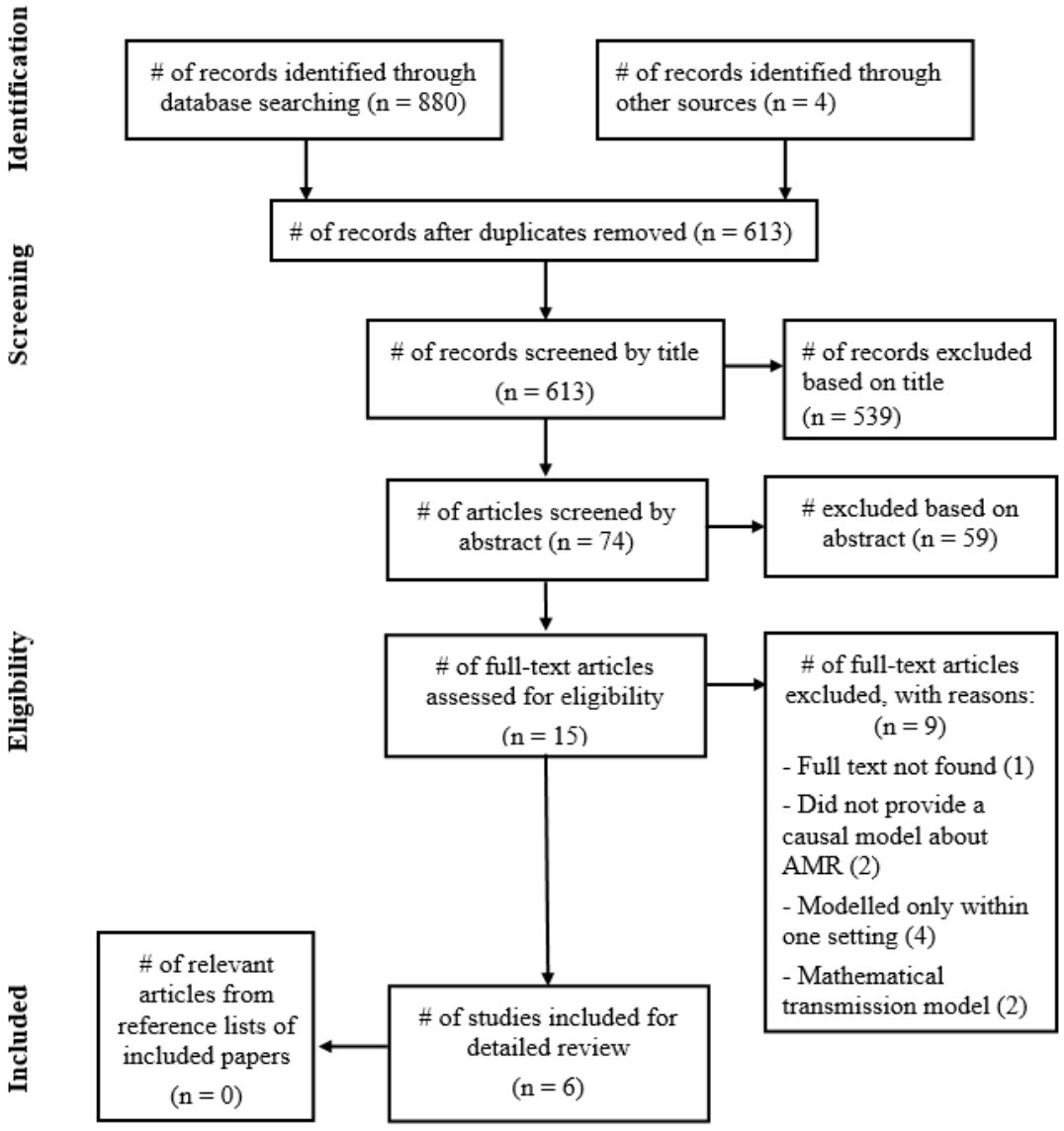

Figure 3.1 Flow diagram of search process and results, based on PRISMA guidelines (Moher et al, 2009)

The search of the System Dynamics Review conference proceedings found a further two records, and two others were recommended or found during previous research. After removal of duplicates, 613 records remained for screening by title. At this point 539 titles were excluded, mostly because they did not integrate more than one dimension of AMR. The resulting 74 articles were screened by reading the abstract. Sixty-one of these were excluded. The main reasons for exclusion at this stage were that the papers did not describe a model of the AMR system (although many did mention two or more of human, animal and environment aspects in passing, and highlight that AMR is a complex problem).

This left 15 full text articles to be assessed for eligibility to be included in the review. Upon reading the full text, only six of these articles were eligible to be included for detailed review. I therefore briefly summarise the nine articles excluded on full text review below.

One abstract (92) was excluded as the full text could not be found. This appeared to be an extension of the study described by Homer *et al.*, 2000. Two mathematical modelling studies relating to the transmission of resistance between food animals and humans (111, 112) were excluded as they did not meet the causal theory criteria. Four articles were excluded from further analysis as they only modelled within one domain or setting (39, 92-94). Two of the papers (86, 87) strongly advocated for a systems approach to learning about and addressing AMR, and discussed the importance of integrating human, animal and environmental aspects of AMR. However, they did not provide cause and effect models of AMR and were therefore excluded. It is worth mentioning that other articles did discuss the idea of AMR as a complex system and involving links between the three areas. However, they did not include *models* of AMR and were therefore excluded.

This process of exclusion left only six papers that closely matched the inclusion criteria for the review. These are shown in Table 3.1 overleaf.

Table 3.1 Characteristics of included models

Reference	Focus (domains)	Model type	Process for building model	Purpose of model
Homer *et al.*, 2000 (39)	Mostly human aspects, some animal aspects	Causal loop diagram (qualitative SD model)	Limited information about process, but involved a group of experts	To display AMR problem structure and policy loops
Cox and Ricci, 2008 (80)	Mainly human and animal (food chain transmission of resistance), with small environment link	Quantitative SD model, with a simple qualitative directed acyclic graph to illustrate	Six proposed causal relations justified by reference to historical trends/the literature	Quantitative risk assessment modelling -to assess likely effects of a ban on animal antibiotic use.
So *et al.*, 2015 (89)	Transmission from livestock to humans, with the environment as one possible pathway	Conceptual model	Not entirely clear. Cites one study	To display pathways of transmission of ABR from animals to humans
Grohn *et al.*, 2017 (88)	Human and food animal aspects	Qualitative model with some SD features	Limited information available	To illustrate boundaries of the food supply system to be modelled
Majowicz *et al.*, 2018 (90)	Human, animal and environment (in context of Canadian food chain)	Qualitative SD conceptual model. High level of complexity	Diagramming of factors impacting, or impacted by, use and resistance along the Canadian food chain. Using group model building and expert elicitation within the author group	To identify stakeholders not traditionally engaged in mitigating AMR who could play a role
Henriksson *et al.*, 2018 (113)	Human and animal (aquaculture) factors. Small reference to environment	Summary conceptual diagram	Identifies main factors behind AM use in aquaculture, providing evidence from the literature to support each. Then combines this information in a summary diagram	Summarise underlying and proximate driving factors of AM use in aquaculture globally. To help identify possible mechanisms for reducing AM use

3.2.1 Design of included models

Three of the models had some features of qualitative system dynamics models (39, 88, 90), one was described as a quantitative system dynamics model (with a qualitative illustrative diagram) (80), and two were linear conceptual models (89, 113). One model was specific to Canada (90), whilst the other models were not specific to a particular country. I will now discuss each in more detail.

Homer et al., 2000

The earliest relevant model was from 2000 in a paper by Homer *et al.* (39). The paper was mostly about modelling bacterial population dynamics, however they did include a diagram illustrating the wider complexities of the problem (Figure 3.2).

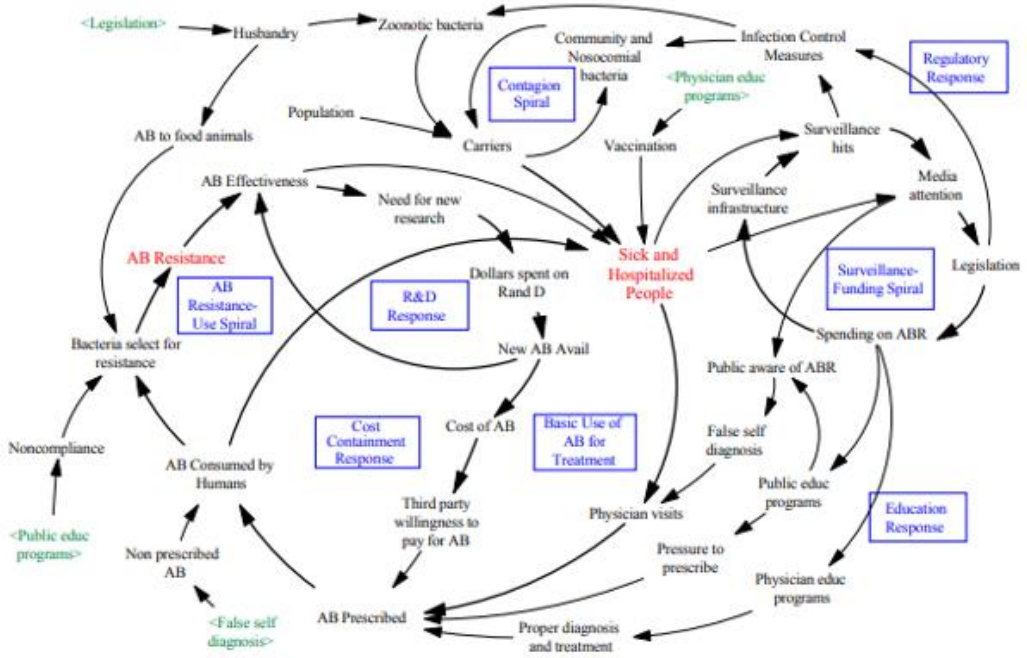

Figure 3.2 Causal loop diagram of antibiotic resistance policy loops (Homer et al, 2000)

This diagram was based on a 1998 meeting between the Infectious Disease Epidemiology and Surveillance Division of the Texas Department of Health (TDH), and the Strategic Decision Simulation Group, which *"assembled a group of experts to begin thinking systemically about the problem of antibiotic resistance and possible policy options at the state and national levels"* (39 p.288). The diagram is policy oriented. It includes policies

such as education and regulation, and simulation modelling was employed to look at specific policy options. Homer *et al.* include a version of the causal loop diagram produced from the meeting, but do not provide details about the model building process. I was unable to find any further information about the diagram or how it was produced.

The model includes human social, political and economic factors involved in perpetuating antibiotic resistance, but also includes a few variables related to animal husbandry and use of antibiotics in food animals. Environmental aspects are not present. Six feedback loops can be identified in the diagram: 'contagion spiral', 'surveillance-funding spiral', 'basic use of AB for treatment', 'R&D response', 'cost containment response' and 'AB resistance-use spiral'. It is not clear whether 'regulatory response' and 'education response' are feedback loops. However, while this diagram represents a causal theory in that arrows between variables represent causal relationships, the exact nature of these relationships (+/-) and the type of feedback loops (reinforcing or balancing) are not specified, which is unusual for a causal loop diagram. This model illustrates that as long as two decades ago, systems modelling was viewed as a potentially helpful way of better understanding antibiotic resistance.

Cox and Ricci, 2008

Cox and Ricci (2008) describe a quantitative system dynamics model of bacterial flows, with the aim of explaining how banning the use of antibiotics in animal agriculture may paradoxically increase resistance in humans (and is therefore implicitly policy oriented) (80). The article begins with a regulatory analysis of precautionary legal requirements, making the argument that precautionary bans of animal antibiotics in Europe were a result of more political will than empirical evidence. The quantitative model consists of six proposed causal relations represented by ordinary differential equations. However, the qualitative diagram used to illustrate the model (Figure 3.2) is a directed acyclic graph (DAG). By definition, a DAG is a causal theory that stops time – it is not dynamic and is not allowed to incorporate feedbacks. Therefore, this diagram may indicate that the principles of system dynamics have not been used correctly to build the model.

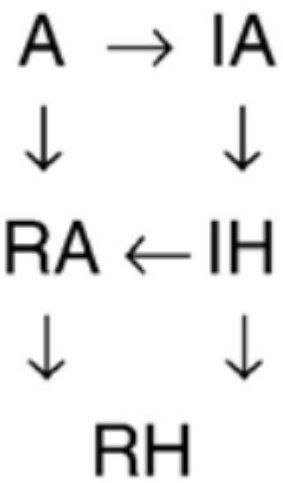

Figure 3.3 DAG of the relationships between antibiotic use in animals and resistant infections in humans (Cox and Ricci, 2008)

The variables involved in this simple model include the fraction of humans with a specific foodborne illness (IH), ill animals (IA), resistant infections in humans (RH), resistance contamination of animal food products (RA), and animal antibiotic use (A). Transmission of resistance via the environment is mentioned as possible links between some of these variables. A set of equations represents this model quantitatively, and indicates that a ban of animal antibiotics can increase resistance in humans, if said ban results in a sufficiently large increase in sick animals, and therefore sick people.

So et al., 2015

So *et al.* (2015) include a linear conceptual model (89). This is a simple overview of transmission pathways of antimicrobial resistance between animals, the environment, and humans (Figure 3.4). The main focus is illustrating how resistance in food animals may pass to humans. Influencing policy does not appear to be an aim of the diagram. The process for developing the model is not described, but it appears to rely on one cited source about cross-species transmission.

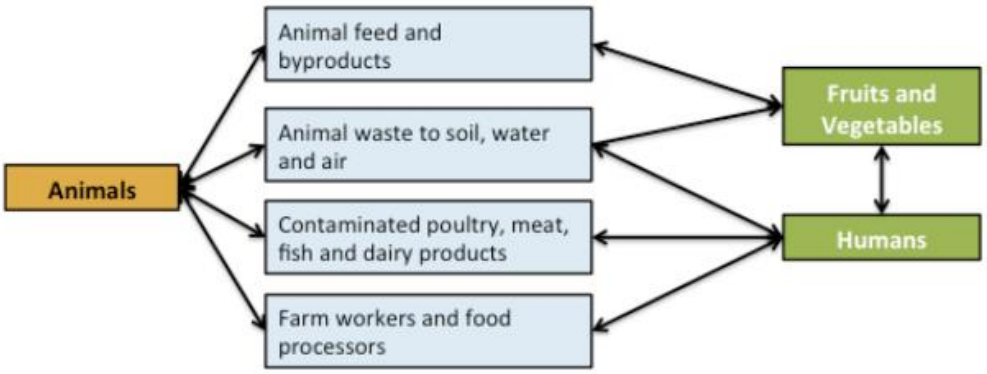

Figure 3.4 Transmission pathways model (So et al., 2015)

Grohn et al., 2017

More recently, Grohn *et al.* (88) described a multi-disciplinary effort to create a framework to analyse the impact of the policy of restricting use of antibiotics in animals – to evaluate how antimicrobial use interventions impact on AMR. A systems approach was decided upon due its suitability for supporting decision-making and evaluating interventions for complex systems. The authors point out that no suitable integrative model of AMR existed that could be used to assess the policy. The authors use a systems approach to understanding drivers of AMR. The paper includes an overview model which met the criteria for this review (Figure 3.5). This is a qualitative model used for the purpose of illustrating the boundaries of their particular research question. It has some characteristics of a qualitative system dynamics model, though it was not described as such (Figure 3.5). The polarities of the arrows, incorporation of feedback and indication of time delays are features of SD, but the feedback loop (relating to media attention and public awareness) is not explicitly labelled. There is some inclusion of policy-related variables, such as 'initiatives of livestock industries'. In later parts of the paper they describe modelling including pharmacodynamic/pharmacokinetic modelling of the exposure of bacteria to antimicrobials, and the likely effect of such selection pressure on AMR in meat (these types of models did not meet the criteria for inclusion in this review). Grohn *et al.* propose bringing these 'subsystems' together using a systems approach.

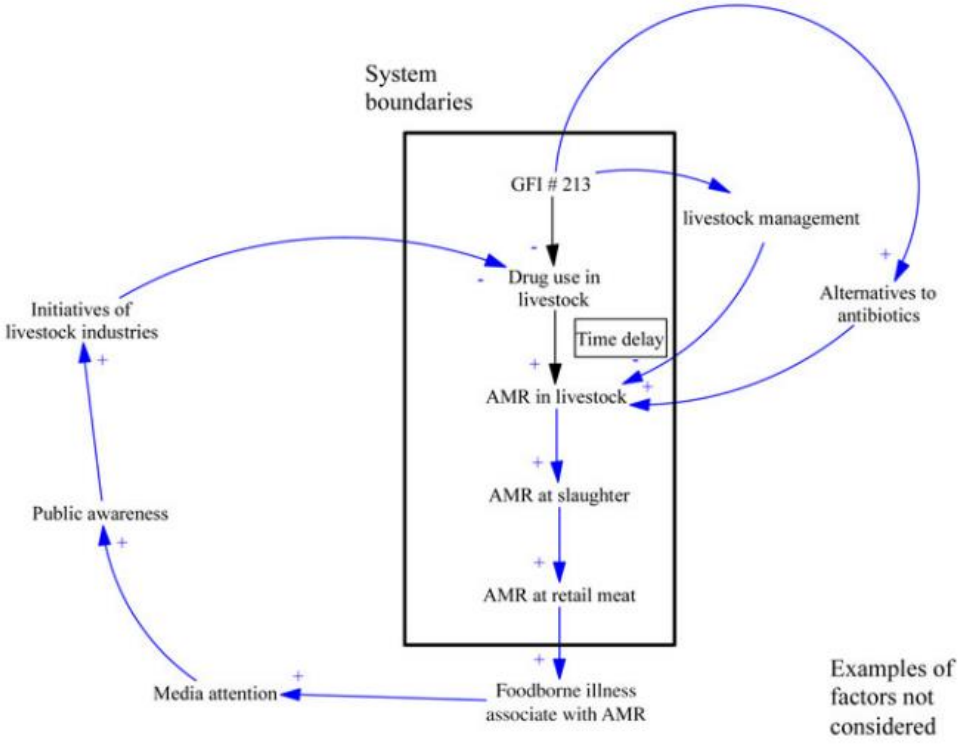

Figure 3.5 Boundary setting system dynamics model (Grohn et al., 2017)

Majowicz et al., 2018

Majowicz *et al.* used a system dynamics modelling methods to diagram factors impacting, or impacted by, antimicrobial use and resistance along the Canadian food chain (90). The authors contextualise AMR as an issue involving people, animals and the environment, but narrow their model focus to the food chain. Variables and relationships were identified using group model building and expert elicitation processes within the author group (90). The purpose of the model was to identify stakeholders not traditionally engaged in mitigating AMR who could play a role, whom researchers and policymakers could work with. This was determined by identifying individuals or organisations who act on the factors in the model.

The process began with a simplistic representation of AMR in the food chain and its links to AMR and human illness, then iteratively added further factors before applying a case

scenario to the draft model. Further refinements yielded the final conceptual model shown in Figure 3.6.

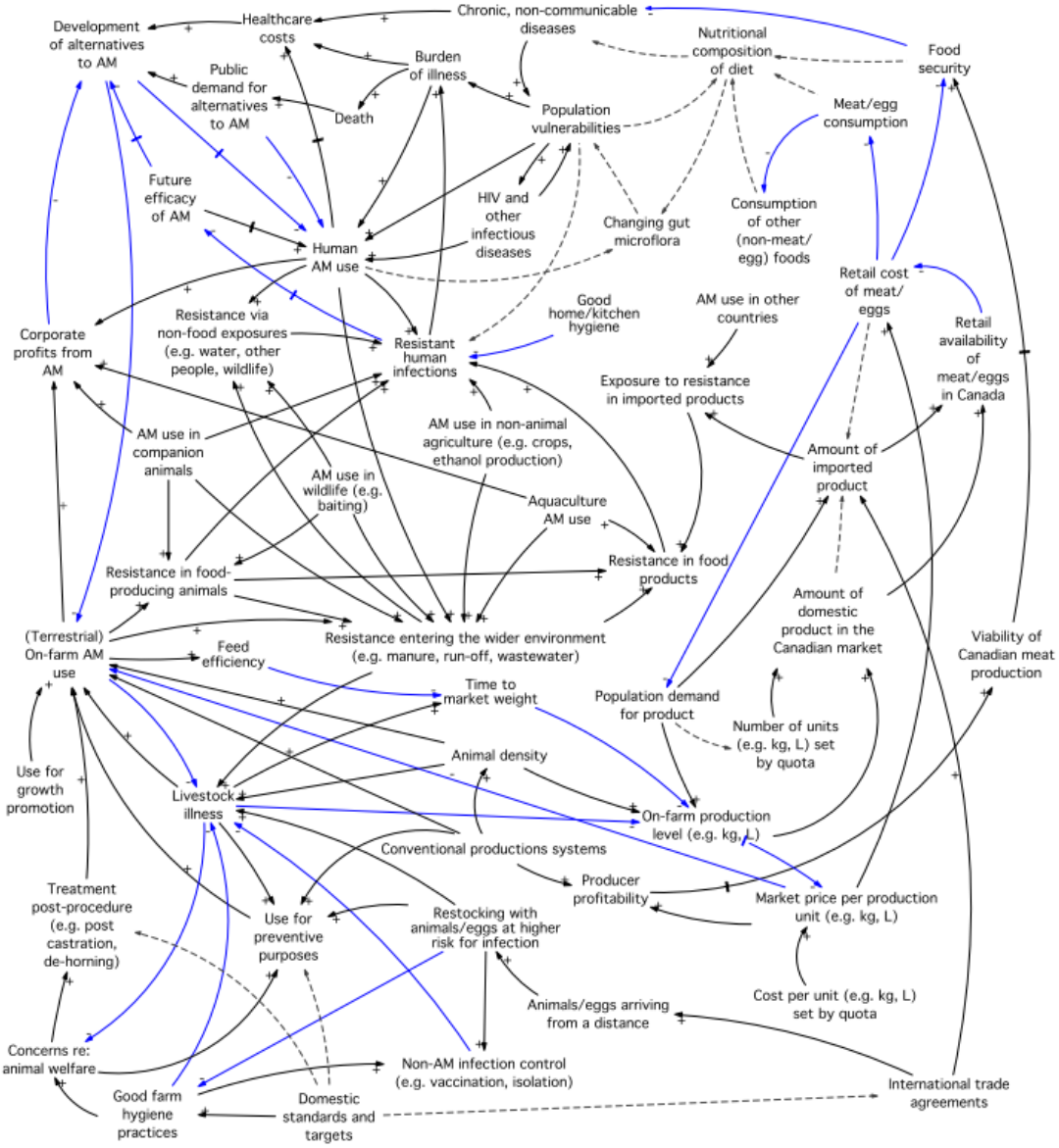

Figure 3.6 Qualitative system dynamics model of AMR in the Canadian food chain (Majowicz et al, 2018)

Although it has been drawn using qualitative SD principles, the diagram does not identify feedback loops (purposeful identification of feedback loops is standard practice in SD modelling). Therefore, it is arguable whether the resulting diagram can be called a true SD model. However, upon close inspection a number of potential feedback loops can be seen within Figure 3.6, for example: population vulnerabilities increases HIV and other infectious diseases, which increases population vulnerabilities (reinforcing loop); on-farm AM use reduces livestock illness, which reduces use for preventive purposes, which reduces on-farm AM use (balancing loop). The complexity of the diagram makes it

somewhat difficult to decipher the relationships and overall message, but it successfully meets its stated purpose of facilitating the identification of a range of non-traditional stakeholders in the issue of antimicrobial use and resistance in the Canadian food chain. The model illustrates complexity and the variety of factors involved, rather than portraying a refined causal theory that can be used to influence policy making.

Henriksson et al. (2018)

Figure 3.7 from Henriksson *et al.* shows a linear conceptual model of inter-linkages between underlying drivers and antimicrobial use in aquaculture through a set of proximate factors (113). The purpose of the diagram is to summarise the most influential underlying and proximate factors driving antimicrobial use (and therefore resistance) in aquaculture. They are structured in a hierarchal manner ranging from the individual animal to international policy level. The model includes an important positive feedback loop between resistance and antimicrobial use (more resistance leads to more antimicrobial use, which leads to more resistance), which is further discussed in text.

The model is based on the preceding text, which identifies the main factors driving antimicrobial use in aquaculture, providing evidence from the literature to support each. This model is not as specific about the nature of the relationships between variables as some of the previous models. It includes some reference to policy being part of the system, e.g. ‘food safety regulations’.

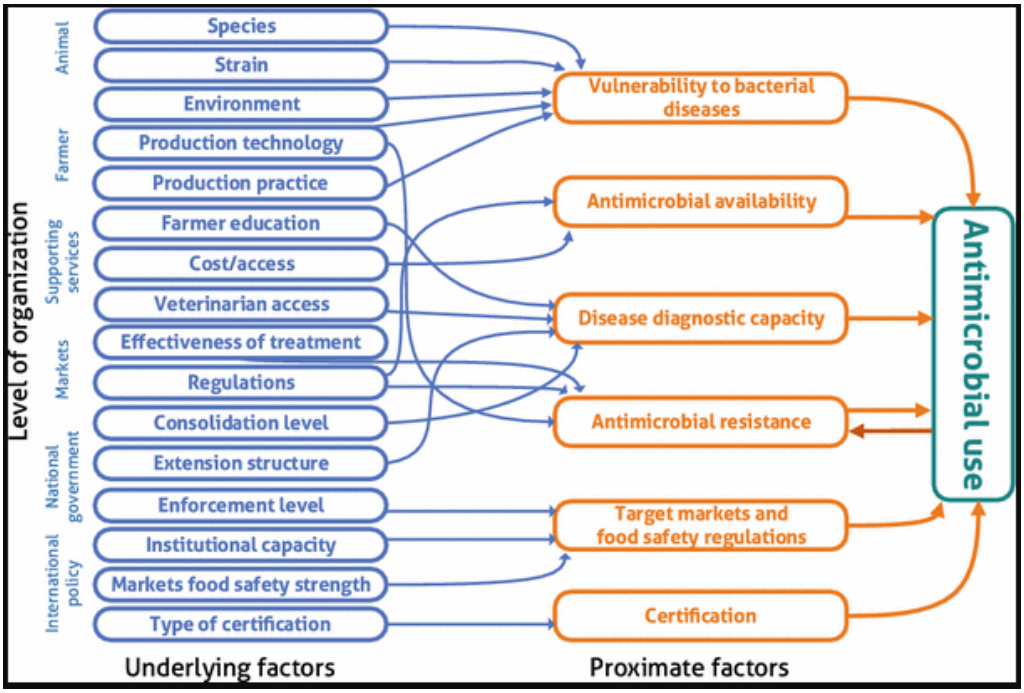

Figure 3.7 Conceptual model of drivers of antimicrobial use in aquaculture (Henriksson et al., 2017)

3.2.2 Domains covered

Most of the models described above focused on the interplay between human and animal domains, with a focus on the food animals (80, 88-90, 113). Homer *et al.* (2000) had the least amount of focus on animals, and the most emphasis on high-level structural factors and policy responses to AMR. The environment domain was under-represented – although four of the models (80, 89, 90, 113) included some reference to the environment, this was not done in detail.

The system dynamics model in Majowicz (2018) includes a multitude of human, animal and environmental factors, with a focus on the first two. A number of these are high level drivers, e.g. 'corporate profits from AM' and 'public demand for alternatives to AM'. The main areas of interest for Cox and Ricci (2008) are the links between human and animal health, mainly via the food chain. Resistance in the environment is not a specific variable in the model, but is discussed as being on the pathway between variables (e.g. *"Conjecture 2, antibiotic use in ill humans leads to increased resistance in the environment and, eventually, in food animals"* (p 468)).

Henriksson *et al.* (2017) focus on antimicrobial use in aquaculture. Their model includes factors that are specific to animals (aquaculture), farmers and higher level services/government/policy (human-related factors). The environment is alluded to in the model in terms of influencing animal vulnerability to bacterial diseases, but further environmental aspects of AMR are beyond the scope of the model. However, it does emphasise in text that AMR gene transmission goes beyond aquaculture, therefore requiring a One Health approach to AMR (113). The text points to an important link between AM use in aquaculture and AMR in humans, particularly as anthropogenic and livestock waste often end up in the aquatic environment.

The model in the paper by Homer *et al.* (2000) mainly focuses on human aspects of the AMR problem, with a small inclusion of some livestock related variables. High-level factors such as 'surveillance infrastructure' and 'dollars spent on R and D' are included. The causal model in Grohn *et al.* (2017) specifically relates to the transmission of antibiotic resistance from livestock to humans (zoonotic factors), with inclusion of wider economic and social variables such as 'alternatives to antibiotics', 'media awareness' and 'public attention'. The causal model in So *et al.* (2015) focuses on the transmission routes of AMR from food animals to humans, with the environment as one possible pathway.

3.2.3 Model quality and validity

Overall there was little attention paid to model validation or describing the basis for the relationships described, undermining the quality of the models. Only two papers described how they arrived at the relationships in their diagram with supporting evidence (80, 113). The others lacked robust validation against the existing literature or routinely collected data. One paper (80) had an explicit discussion of the validity of their model, and one (90) mentioned that further work would be needed to refine and validate the model.

It is difficult to comment on the validity of the SD model included in the paper by Homer *et al.* (2000) due to the lack of information about the origins and process of building the model, beyond a brief mention of simulation modelling. The quality of the model is limited by the fact that traditional causal loop diagram symbology is not used; they omit to assign polarities to the relationships between variables, and do not specify the types of

feedback loops. Despite this, the diagram provides useful insights into the variety of perspectives on high level drivers of AB resistance, and highlights feedback loops that are not recognised in other articles.

Cox and Ricci (2008) produced a Directed Acyclic Graph as part of their quantitative risk assessment. It seems to have been useful for its intended purpose, which was to inform a quantitative model to evaluate the possible impacts of banning animal antibiotics on human health. The assumptions behind the differential equations of the model are justified with reference to the literature. They make formal attempts to validate the model through testing implications of the model by comparison with historical data. The results of these tests reportedly support their conclusions but the authors note that as better surveillance data becomes available it will be necessary to re-test and refine the model (80). The model is useful in that it provides an overview of some key components and relationships linking human and animal health and resistance. However, given the small number of variables (five) in the model, it does not capture the complex or wider drivers of the problem. The complexity of the modelled equations make it difficult for a non-statistical expert to interrogate the nature of the relationships being modelled, limiting its ability to be validated or increase wider systems understanding.

The conceptual model in So *et al.* (2015) is useful in that it highlights some simplified pathways of resistance transmission. Its quality and validity may be limited because it is based on only one cited source, but it does correspond with wider literature in terms of possible transmission pathways.

The model in the Grohn *et al.* (2017) paper is useful in providing a transparent indication of what factors the authors consider are 'within scope' in later modelling steps. Some of the factors of interest were well described in the following text, and a variety of complex models were used to address these in later steps, including pharmacokinetic/dynamic modelling techniques. Grohn *et al.* (2017) devote some effort to discussing sources of model uncertainty, but this is not done specifically in relation to the model discussed in this thesis. Later in the paper the 'factors not considered' are described in more detail, though references are not provided to justify their inclusion in the wider model.

The model in Majowicz *et al.* (2018) is useful in that it meets its purpose of aiding identification of non-traditional stakeholders who could be involved in mitigating AMR. It provides a transparent starting point for more in-depth model building (90). A factor that may weaken the validity of the model is that the relationships identified are based solely on the expertise of the author group. They acknowledge their perspective is biased towards public health, foodborne disease, veterinary medicine and livestock factors, and comment on the need to involve other kinds of experts to improve confidence in the model and validate it (90). A further recognised limitation is that constructing a higher level systems view of the problem has trade-offs with nuance and detail (90).

Confidence in the model by Majowicz *et al.* is diminished by the fact there is no discussion of justification of the particular variables included and the nature of the relationships between them, beyond describing the process for building the model. However, the authors applied an example case scenario to their initial draft model to aid further refinement, which helps build some confidence in the model. The broader usefulness of the model is limited by the fact they did not go as far as specifying feedback loops in the diagram, and the complexity of the 'spaghetti style' diagram also limits comprehension. The type of SD model is not specified, other than to say it is a 'conceptual model'. They acknowledge that future modelling steps will need to include consultation with a wider group of experts, and validation processes.

The model in Henriksson (2018) is a summary diagram of factors discussed in depth previously in the paper. The links between factors can be easily followed and understood and are supported by information and references given in the text. The model's clear structure makes it a useful summary diagram about causal pathways leading to AM use in aquaculture. However, as the types of variables included in the model are quite broad and the exact nature of the relationships between the variables are not specified in the model, it would be difficult to formally validate the model. It seems to be a summary model rather than a model intended to be tested and verified.

3.3 Summary and discussion of review results

The aim of the literature review was to identify previous research that has modelled the AMR system, integrating human, animal and environmental dimensions of the problem

in a way that represents a *causal theory.* Models that might have policy relevance were of particular interest. Only six studies met the criteria for inclusion in the review. Most were focused on modelling the transmission of antimicrobial resistance from food animals to humans. Four models (80, 89, 90, 113) included some reference to the environment, but not as a significant model component.

Four models (39, 80, 88, 90) were reported to be system dynamics models of some kind, or exhibited some characteristics of an SD model. However, none of these would meet the criteria expected for the presentation of an SD model. Purposeful identification of feedback loops was particularly lacking. One of these models (80) was a quantitative system dynamics risk assessment model which used a DAG to illustrate the model qualitatively, which is at odds with SD goals of representing feedbacks in a system. The other two models were linear conceptual diagrams (89, 113). One of the models represented and discussed a feedback (113).

Five of the six models (all but So *et al.*, 2015) were policy oriented in some way; some aimed to assess the results of policy changes, some were aimed at eventually improving policy, and some included policy related variables. However, few specific policy inferences were drawn. The main policy statements were around the need to include non-traditional stakeholders in AMR policy making (90) and to consider unintended consequences of policies that restrict use of antibiotics in food animals (80).

None of the articles identified themselves specifically as One Health (though some discussed the importance of a One Health approach), and none mentioned EcoHealth. Two articles specified that model development involved participation of a group. However, one (Homer *et al.*, 2000) did not specify what kind of 'experts' were involved in building the model and the other (Majowicz *et al.*, 2018) relied on expertise within the author group.

Overall the quality of the modelling studies was quite poor. Formal attempts at establishing and reporting model validity were generally lacking. Several models were reported to have used SD modelling methods, but did not meet several of the characteristics required for SD models. Many of the models were not the main focus of

the papers, and therefore did not have much information given about them, which made quality and validity assessment difficult. Explicit assessment of model quality and validation was rare, which seems to be in keeping with the situation of systems-modelling techniques for public health research more broadly (28).

Of the many articles written about antimicrobial resistance, an increasing number are calling for a systems approach to address the problem. However, most AMR models have tended to focus on a single domain (90) and the biological aspects of AMR (97). In investigating this area further, this literature review found very few models that integrate two or more of human, animal and environment AMR dimensions into a causal theory. None considered all three comprehensively. The environment dimension is particularly under-represented in the models found in this review, though it is increasingly recognised as an important reservoir of AMR.

Despite the increasing literature on the need for integrative approaches to AMR, and recognition of AMR as the 'quintessential' One Heath issue (7 p.1), none of the models found in this review specified a One Health or EcoHealth approach. These are two holistic approaches to human, animal and environmental health that deserve more attention in AMR modelling. There is also lack of AMR models that are specific to particular countries or contexts. Whilst the models found in the review may be somewhat generalisable, policy options that work are likely to vary by context, as the main influences on AMR could vary by country. It would therefore be beneficial to have a New Zealand specific model of AMR.

In this review, the most formal models were system dynamics models. This illustrates the potential usefulness of a system dynamics approach to modelling, which could be explored further. However, there is room for improvement in this area in terms of expanding the scope of the models, and a need for better use of standard SD language and symbology. Explicit focus on feedback loops would be beneficial in helping identify and address the main drivers of the problem. In addition, models that balance the need for both simplicity and comprehensiveness are needed to provide confidence in model validity while maximising understanding to support policy-making. Participatory

approaches to modelling appear to be under-utilised and could be built on in the area of AMR. Increased focus on validity of the models is also needed.

3.4 Summary

This literature review found very few studies that include causal model of AMR incorporating two or more of human, animal and environment dimensions. The small number of models found tended to focus on AMR transmission in the food chain. The most formal models tended to report using system dynamics modelling methods, but there is room for improvement in correctly applying SD principles and methods, as well as a need for models that consider quality and validity more explicitly. Participatory approaches were under-utilised.

Based on these gaps in modelling efforts, I have chosen to build an integrated model of AMR in New Zealand using a participatory system dynamics approach, purposely underpinned by One Health and EcoHealth principles. Next, the methodology chapter will further describe and justify the suitability of such an approach to better understand AMR in New Zealand.

4 Methodology chapter

The previous chapters have outlined the complexity of antimicrobial resistance and identified the need for more integrative models of the problem. This chapter discusses the methodological principles that inform my research approach to better understand AMR in New Zealand. To begin this chapter, I explain my values and personal approach to research. Next, I discuss the One Health and EcoHealth research paradigms, which both inform this work. I particularly focus on how my project relates to the principles of EcoHealth, especially the principle of systems thinking. To conclude I focus on how a participatory system dynamics approach can operationalise these aforementioned theoretical underpinnings.

4.1 Personal research approach

I subscribe to the qualitative view that science occurs within a wider context and is influenced by the subjectivities of the researcher. Thus, it is important that I am clear about the values and theories that inform my approach to this work, as this will influence the types of questions asked and how they are answered (114). My background is in Medicine and Geography, and now Public Health. I have long-standing interests in both health and environmental issues, and the interconnections between them. These interests and areas of study have instilled strong values relating to environmental sustainability, equity, a holistic concept of health, and questioning of existing power structures. My definition of health is based on that of the World Health Organisation (1948): "*a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity*" (115 p.1) However, given the limitations of this definition (116), I extend my ideas about health to take into account the Ottawa Charter's focus on enabling people to achieve their aspirations and cope with changing environments; the idea that health is a resource (115). Further, I take the public health position that individual health and well-being is in large part determined by factors upstream (26), including social, economic and environmental dimensions (117).

Ontology refers to our ideas about the nature of reality, whilst epistemology consists of ideas about *how* we know what we know (118). Positivist and constructivist paradigms are thought by some to sit at opposite ends of a spectrum of ontology and epistemology

(23, 119). Positivist ontology assumes that a single reality exists, and that scientific enquiry can be used to come to know this reality (23). Its epistemology assumes that scientific enquiry results in objective knowledge about that reality. On the other hand, constructivist positions contend that multiple, socially constructed realities exist (23). My position is that there is an external reality 'out there' (moderately positivist ontology (23)) but that it is important to understand the diverse subjective understandings of reality. Therefore, in terms of epistemology I lean more towards the 'constructivist' methods of building knowledge. I identify with the 'critical realism' theoretical position, which is a 'middle ground' (120) that *"accepts the existence of an external reality, but that it can only be known in subjective terms"* (23 p.5)

4.2 One Health and EcoHealth approaches

This study is underpinned by One Health and EcoHealth research paradigms. Both incorporate holistic, systems-level conceptualisations of human health and its relationship with the health of animals and the environment, recognising the complexity of linkages between these three domains (21-24). They are two of several fields that operate at the interface between the health of ecosystems, humans and animals (24). An integration of these paradigms is shown in Figure 4.1 (overleaf).

The smaller circles represent that the wellbeing of humans, domesticated animals and wildlife are closely overlapping. They are set within the context of human-created environments and human social, political and economic systems, which are embedded in and determined by the health of natural ecosystems (21, 117). Both EcoHealth and One Health approaches support using systems thinking for understanding and addressing health problems, and both value the integration of scientific disciplines through inter and trans-disciplinary research and collaboration (21, 22, 24, 121). However, their origins and focuses are different (23, 122). These holistic approaches to health are thought to be promising for dealing with 'wicked problems' such as climate change, food system problems, and built environment issues (122). The following sections will describe One Health and EcoHealth in more detail, and how they are applied in this research.

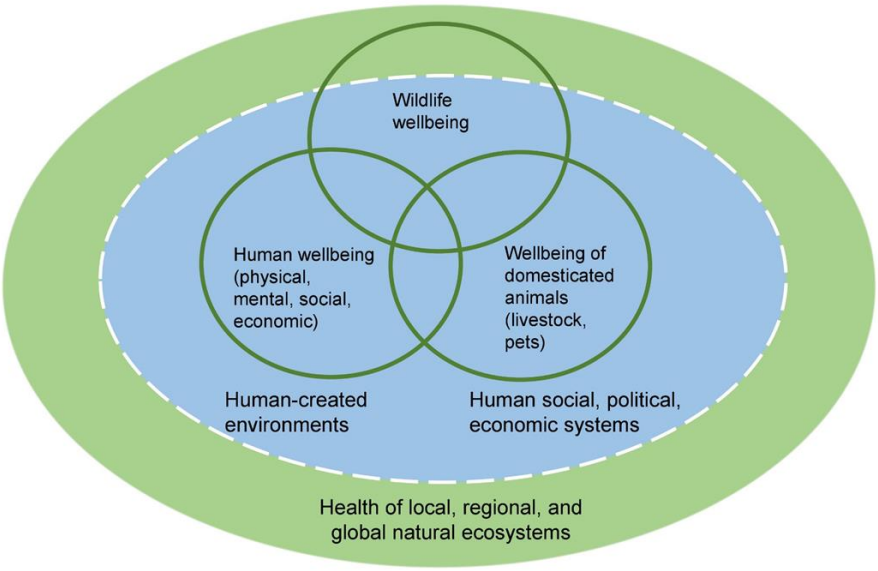

Figure 4.1 One Health/EcoHealth integrating framework. Acknowledgments to Patricia Priest and Alex Macmillan

4.2.1 One Health

One Health can be defined as collaboration between multiple disciplines at a range of scales to improve the health of people, animals and the environment (123). One Health addresses issues at the intersection of human, animal and environmental health (122). Biological threats are particularly referred to as needing a 'One Health' approach for prevention and mitigation (124). One Health research was historically health-science driven, and mainly focuses on the links between humans and animals (22), particularly addressing biomedical questions relating to zoonotic disease threats (21, 22). The main actors involved in One Health tend to be veterinarians and public health practitioners, though involvement of other disciplines is growing (22, 23). The role of the environment is increasingly considered, but not as habitually as in EcoHealth (23, 121). In practice, One Health tends to emphasize positivist aspects of veterinary and medical disciplines (23), but this is changing.

The background chapter established that the complex issue of AMR has links to all three of the One Health domains. It is increasingly recognised that a 'One Health' approach to understanding AMR, that appreciates the complexity of interactions between human, animal and environmental health, is necessary (125-127), and the action plans of several

countries and international agencies reflect this (21, 128). New Zealand's Action Plan on Antimicrobial resistance (129) was developed by an inter-disciplinary Working Group, evidencing an approach informed by One Health.

In this research I have recognised AMR as a One Health issue by involving stakeholders from the three domains: human and animal health, and the environment. As will be outlined in the methods chapter, stakeholders were specifically selected to gain information about these three interconnected areas. As well as regarding One Health approaches as fundamental to tackling AMR, there is also recognition by some that involvement of economic and social sciences is also required (7). In this research I have used EcoHealth principles to help provide a complementary approach and further guide my methodological choice.

4.2.2 EcoHealth

Many of the human health and environmental challenges facing the world today are interlinked, urgent, large-scale, multi-dimensional, complex, and uncertain (130). Integrative approaches are needed to overcome the limitations of traditional reductionist science in dealing with such complexity (25, 131). Ecosystem approaches to health seek to achieve this, and underpin my approach to this study. EcoHealth is an evolving field of research and practice (117) centred on understanding the reciprocity of relationships between human health and ecosystem health at a range of scales (22, 117, 120, 132). In essence, EcoHealth assumes that: *"humans, and our social and economic systems, are embedded within ecosystems, and that these coupled social–ecological systems behave as complex systems"* (25 p.19).

The EcoHealth paradigm emerged in Canada in the 1990s as the need for new ways to address complex, persistent and inter-related health challenges was recognised (117, 130). EcoHealth recognises that single-sector, non-participatory approaches and technological fixes are ill suited for dealing with these kinds of problems (130, 133). It adopts a broader conceptualisation of health than One Health, and has been strongly influenced by the sustainable development movement (122). Although animal health is included in its scope, it is not generally the focus (117). EcoHealth places more emphasis on social science and humanities disciplines than One Health, as well as acknowledging

the value of local and Indigenous knowledges (134). It is common for EcoHealth research to proceed in an iterative way, involving knowledge generation, action and reflection (130). According to Albrecht (2008), EcoHealth is underpinned by the critical realism philosophy. EcoHealth's transdisciplinary focus acknowledges the existence of multiple subjective socially constructed realties (23). It therefore suits my own research approach.

The principles and spirit of the 1987 Brundtland report (135) – social justice, participation, and equity – strongly inform EcoHealth thinking and practice (122). EcoHealth seeks to improve human health while fostering thriving and resilient communities, alongside environmental sustainability (117, 130). Use of a range of integrative approaches and methodologies reflect the complexity of the public health issues being addressed, which is considered by some to be a significant advance in public health research (117). There is growing evidence of the effectiveness of EcoHealth approaches for addressing health challenges that are systemic, particularly when vulnerable populations are affected (117). It has often been focused on helping manage health and environmental issues in developing countries (130).

Charron (2012) laid out a set of six widely cited 'guide posts' that inform EcoHealth research. The first three principles (systems thinking, transdisciplinarity and participation) relate to the ideal process of the research, whilst the other three (sustainability, gender and social equity, and knowledge-to-action) are more focused on the intrinsic goals of EcoHealth research (130). These are now discussed in more detail.

1. ***Systems thinking:*** EcoHealth approaches seek to understand the complex, multidimensional relationships involved in human and ecosystem health (132), acknowledging that ecological, socio-cultural, economic and governance factors are involved (130). Fundamentally, systems thinking seeks to understand how things are connected to each other to form the whole (136). Systems thinking is a diverse field in its own right covering hard, soft and critical traditions (137).

2. ***Transdisciplinarity:*** EcoHealth approaches recognise that academic perspectives are necessary but not sufficient for understanding health within

social-ecological systems (130), and that development of *"socially robust"* (133 p.11) solutions requires integration of different scientific disciplines (inter-disciplinary) and non-scientific perspectives, such as community, policy and industry perspectives (132, 138). This necessitates engagement of researchers with community members and decision-makers, including people with informal influence due to their knowledge, experience and reputation (130, 133).

3. ***Participation:*** Related to the concept of transdisciplinarity, participation further emphasises the value of developing a shared understanding of problematic situations and locally rooted solutions, aiming for cooperation within and between groups and improved appreciation of alternate worldviews (130, 133, 139). EcoHealth projects should consider local knowledge, concerns and needs (133). Engagement of stakeholders increases the likelihood of gaining new insights and successfully implementing context-appropriate solutions (130, 133).

4. ***Sustainability:*** Given that EcoHealth is based on the assumption that ecosystem health is a fundamental requirement for current and future human-wellbeing, it posits that changes resulting from research ideally should be both environmentally and socially sustainable (130).

5. ***Gender and social equity:*** EcoHealth considers unfair impacts on disadvantaged groups in societies (130) and is oriented towards reducing inequities (132). However, Charron (2012) acknowledges that truly addressing inequity, rather than simply commenting on it, is difficult.

6. ***Knowledge-to-action:*** Knowledge generated in the iterative process of EcoHealth research is aimed at achieving real-world change that creates better environments for supporting human health (130). That is, the application of knowledge is very important. 'Research-action cycles' acknowledge the need to react to continually changing situations and new knowledge (130).

The principle of systems thinking is particularly prominent in my research, so will be elaborated on next.

4.3 Systems thinking

As highlighted by EcoHealth approaches, in a world that is highly interconnected and rapidly changing, integrated approaches to dealing with complex problems are needed (25, 123). Many public health challenges are complex dynamic problems (27, 136), characterised by multiple interacting variables, diverse values and concerns of people involved, changing contexts, and changing patterns over time (26, 136). Systems thinking is an approach to problem solving (140) that views the world as a complex system (107) and considers how things are connected within the broader 'whole' (136, 141). In systems that give rise to complex problems, actors such as policy makers, providers, organisations and communities interact in dynamic and sometimes unpredictable ways (27). Dynamic systems consist of interconnected material and immaterial elements, which change throughout time and exhibit patterns such as growth, decline, oscillation and overshoot (140, 142).

Systems thinking has origins in a variety of disciplines, as diverse as: biology, anthropology, physics, psychology, mathematics, management and computer science (136). As a result, there are many theories, methodologies, methods and tools covered by the field of systems thinking (26, 136). Some examples of systems thinking methods and tools include complex adaptive systems, system dynamics, agent-based modelling, network analysis, discrete-event modelling and cybernetics (27, 143). Like EcoHealth, systems thinking approaches often feature inter-disciplinary and multi-disciplinary work, including involvement of the social sciences (107, 136, 144). Systems thinking aims to support shared decision making (141), often by explicit inclusion of stakeholder groups affected by the research alongside the researchers (transdisciplinarity) (136, 141). Some systems methodologies involve the building of quantitative models that allow simulation, whilst other approaches are more qualitative and action-based (28).

Although there are perhaps more than 1,000 methods and methodologies in the systems field, *"making sense of inter-relationships"* (141 p.34) is a foundational concept for all (145). The inter-relationships between parts of a system is the focus, rather than the

individual components themselves (140, 142, 145) – a contrast with traditional reductionist approaches that seek to understand individual components in detail (27). Systems thinking explores how things are connected, and the effect of these causal links (145). These interactions are often complex and non-linear in nature (146). Other important concepts include recognition of the diversity of perspectives different people hold regarding a system, and the impact of value judgements and power dynamics in how issues (and their possible solutions) are framed (145). Systems science methods are useful for considering nonlinear relationships, unintended effects of interventions, and time delays (143). Table 4.1 illustrates some of the differences between the classical approach to problem solving and the systems thinking approach (140).

Table 4.1 Classical versus systems thinking approaches to problem solving (Adam and de Savigny, 2012)[2]

Classical approach	Systems thinking approach
Static thinking Focusing on particular events	**Dynamic thinking** Framing a problem in terms of a pattern of behaviour over time
System-as-effect thinking Viewing behaviour generated by a system as driven by external factors	**System-as-cause thinking** Placing responsibility for a behaviour on internal actors who manage the policies and 'plumbing' of the system
Tree-by-tree thinking Believing that really knowing something means focusing on the details	**Forest thinking** Believing that to know something requires understanding the context of relationships
Factors thinking Listing factors that influence or correlate with some result	**Operational thinking** Concentrating on causality and understanding how a behaviour is generated
Straight-line thinking Viewing causality as running in one direction, ignoring (either deliberately or not) the interdependence and interaction between and among the causes	**Loop thinking** Viewing causality as an on-going process, not a one-time event, with effect feedback back to influence the causes and the causes affecting each other

Source: Adam and de Savigny (2012), modified from Richmond (2000)

[2] Reproduced from Adam and de Savigny, 'Systems thinking for strengthening health systems in LMICs: need for a paradigm shift', Health Policy and Planning, 2012, Issue suppl_4, p. iv1-iv3, by permission of Oxford University Press.

Systems thinking offers an approach improving decision making in complex contexts (147). Donella Meadows, a pioneering systems thinker, wrote:

> *"Once we see the relationship between structure and behaviour, we can begin to understand how systems work, what makes them produce poor results, and how to shift them into better behaviour patterns"*(148 p.1).

Systems approaches have been particularly popular for natural resource management and addressing unsustainable consumption since the publication of the seminal work *The Limits to Growth* (149) in 1972 (31, 141). Systems science approaches are said to hold great potential for dealing with the dynamic complexity of many public health and health system issues (122, 136, 140, 143, 144, 146, 150). Examples of situations where systems science has been applied to public health include simulation modelling of Type 2 diabetes (151), assessment of the effectiveness of policies aimed at reducing smoking prevalence (152), and demonstration of how a focus on curative medicine crowds out prevention (153). A 2015 systematic review of the applicability of systems thinking to public health found many articles that discuss the potential of systems science, but fewer described *how* this could be implemented (28). The review found 36 papers that described systems modelling examples of relevance to public health, of diverse quality (28).

It has been observed that many public health interventions fail to achieve their goals because they are made using compartmentalised, reductionist approaches rather than comprehensive, interdisciplinary, whole-system perspectives (27, 136, 140, 150). Seemingly-obvious policies that seek to improve public health and human welfare often fail, or paradoxically worsen the problems they aim to address (a phenomenon called 'policy resistance') (107, 143, 147). For example, the use of antibiotics to treat infections has accelerated development of AMR, which undermines our ability to deal with communicable disease (147). A number of factors may contribute to policy resistance, including poor understanding of the system and narrow conceptualisations of cause and effect (107). As our actions alter the state of the system, other actors may react to restore balance, or our actions may have unintended consequences (107, 142).

Systems thinking generally involves the creation of a model – a compact representation of how a phenomenon or system is understood (136). Models have a variety of uses beyond the commonly-considered purpose of 'prediction' (154). According to Epstein (2008), some of these include: explaining how things work, testing of policy interventions, identification of areas where more data is required, raising new questions, making assumptions explicit, testing hypotheses, and calibration against real data (136, 154). Systems thinking aims to create models that provide a robust and useful perspective on the inner workings of complex problems. Simulation modelling in particular may hold high potential for improving health (91). Advanced system models that allow simulation can help identify important leverage points where interventions are most likely to have the greatest impact (28, 144, 155), and allow designing and testing of policies in a way that is safe and inexpensive (107, 136, 156).

4.3.1 Participatory system dynamics

System dynamics (SD) modelling is a systems thinking methodology that particularly highlights the principle of inter-relationships (157) and has been identified as a suitable approach for dealing with and addressing the dynamic complexity that characterises many public health issues (150). Of the AMR models discussed in the literature review, those featuring system dynamics models were most common, and represent work that can be built on further. In addition, system dynamics is particularly useful for identifying feedback loops that govern problems, and helping to identify high-leverage policies that can make helpful lasting change (107, 150). SD modelling processes involve developing causal diagrams and policy-oriented simulation models, so that alternative policies and scenarios can be tested systematically (150, 158).

As with the wider field of systems thinking, SD is useful in situations of dynamic complexity: where there are delays between causes and effects, actors in systems have multiple goals and interests that may conflict with each other, and interventions can have unintended consequences (150). System dynamics modelling has therefore been identified as a suitable approach for dealing with and addressing the dynamic complexity that characterises many public health issues (150). There is increasing literature promoting the value of SD modelling to aid policy making, but its practical application thus far has been limited (159). However, it has been used since the 1970s in relation to

population health (150), with success in addressing epidemiological issues, health care capacity and delivery, and patient flow management (150), as well as HIV and diabetes (107). It has also been applied to topics such as commuting modes (108), tobacco control (144) and obesity (160, 161). There are examples of studies using SD for public health policy or healthcare policy (159) for health topics including smoking cessation (162), disease screening (163), mental health issues (164), and pharmacotherapy treatment for opioid dependence (165).

The theoretical assumptions of system dynamics modelling may make it a useful way of converging One Health and EcoHealth, as: *"its critical realism underpinnings offer users a means of reconciling the belief in an external reality and the subjective nature of knowledge"* (23 p.2). SD suits my appreciation for both quantitative and qualitative methods. It aligns with my belief that health, equity and sustainability are intricately connected, and that taking well-considered action to improve one can have co-benefits for the others, while reducing negative unintended consequences. It allows me to occupy 'the middle ground' on the spectrum between positivist and constructivist leanings, seeing value in both. System dynamics is a particularly appealing type of systems science because it can be suitably employed for participatory model building (159).

System dynamics has long recognised the value of modelling with 'problem owners' (166); inclusion of multiple perspectives improves the quality of decision making and is more democratic (167). Participation in system dynamics historically tended to involve inclusion of clients in business modelling efforts (166, 168), and was thus fairly technocratic. However, it has also been used to support better democratic decision-making, including fostering shared understanding and consensus on management of complex environmental issues (31, 104, 166, 169-171), such as water resources planning (172). In more public health specific applications, pSD has been used to assess the interactions between housing, energy and wellbeing (158, 173), reducing alcohol-related harm (174), cardiovascular disease prevention (175), and emergency care (163). Stakeholder involvement in modelling processes improves the richness of models, fosters social learning and consensus, and builds ownership of the model and commitment to the recommendations arising from it (31, 104, 168, 169).

Participatory modelling has been proposed as a useful tool for enabling One Health integration of stakeholders in practice (20). Further, it has been recommended for operationalising the principle of systems thinking that is common to both One Health and EcoHealth (30). In order to deal with complexity, integrated approaches to health (such as One Health and EcoHealth) need to be iterative, adaptive and participatory, and participatory modelling provides a practical way for meeting these requirements (30). Participatory modelling is transdisciplinary and facilitates knowledge sharing, knowledge generation, negotiation and planning (30), by allowing integration of various types of information (31). The process of model building helps stakeholders to clarify their own mental models of the problem, appreciate the perspectives of others, and build an enhanced understanding of the system (31). In other words, participatory modelling enables me to operationalise some of the key principles of EcoHealth (participation, transdisciplinarity and systems thinking) in this research.

A classic 'heuristic' of participatory system dynamics (pSD) modelling involves an iterative process of developing a qualitative understanding of a system (involving the development of a causal loop diagram, described in section 5.2.1), followed by conversion to a quantitative model, incorporating data and allowing simulation. This improves the causal theory and facilitates understanding of the impacts of policy decisions. Performing the whole process was out of scope for this thesis. I therefore set the foundations for a participatory system dynamics approach by establishing a diverse stakeholder group and developing a preliminary set of causal loop diagrams.

4.4 Summary

This research is underpinned by One Health and EcoHealth, two integrated approaches to health that recognise the value of systems thinking and transdisciplinary work. Participatory system dynamics modelling, my chosen method, sits well with the values of these underpinning approaches and has been suggested as a useful way to operationalise systems thinking and One Health in practice. The next chapter describes the methods used to build a qualitative system dynamics model of antimicrobial resistance in New Zealand, with involvement from a diverse range of stakeholders.

5 Methods

This project used a participatory system dynamics approach to develop a qualitative model of AMR in New Zealand, building on AMR science, policy, community, clinical and industry knowledge. It aimed to identify feedback loops that drive the behaviour of the system. The project was participatory in that interviews with diverse stakeholders with expertise about AMR provided the basis for identifying variables in the model and the relationships between them. In this chapter I describe the participatory system dynamics (pSD) process and explain causal loop diagrams and cognitive mapping. I then outline the process for stakeholder selection and recruitment, data collection (interviews) and data analysis (cognitive maps, thematic analysis, and development of causal loop diagrams). Ethical aspects of the project are discussed at the end of the chapter.

5.1 Participatory system dynamics process

According to Sterman (2000), active participation of decision makers in the development of a model is essential for effective learning to occur (107). Addressing public policy problems generally requires consensus, or at least accommodation (139), among diverse stakeholders, so group model building processes are a key part of SD methods (150). I am building the foundations for a participatory approach by identifying and recruiting transdisciplinary stakeholders and taking the first steps to elicit their individual mental models. Participatory system dynamics modelling generally involves three stages (Figure 5.1)[3]: preparatory activities, modelling workshops, and follow-up activities (166). In this research I complete stage one (preparatory activities), which constitutes an analysis of stakeholders who should be invited to take part, and a preliminary assessment of stakeholder perceptions of the problem (166). Interviews with stakeholders are useful for building rapport with participants and for building a preliminary SD model (166). The qualitative CLDs are a crucial first step in the model building process. The next steps would involve participatory workshops and development of a quantitative model for simulation.

[3] Reprinted/adapted by permission from Springer Nature: Springer International Publishing, 'Environmental modeling with stakeholders: Theory, methods, and applications' by Videira et al, 2016.

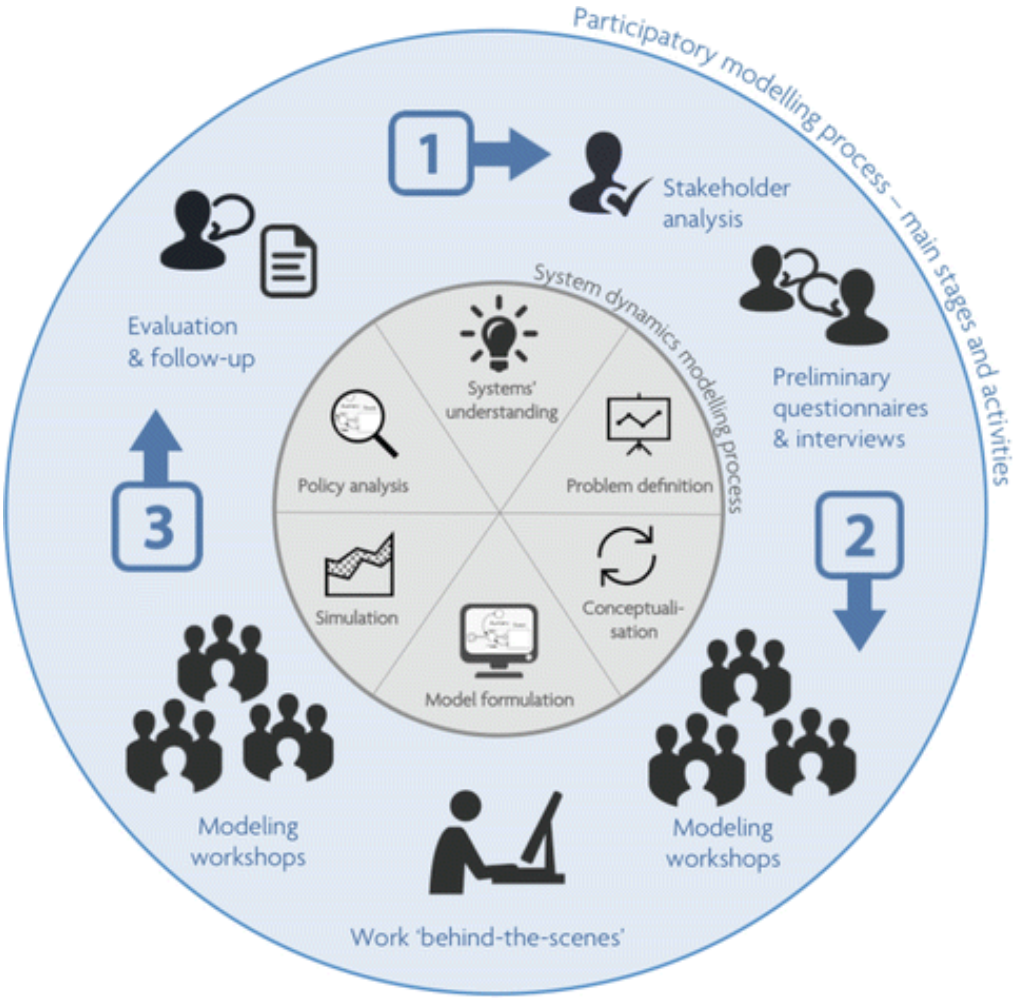

Figure 5.1 A generic participatory system dynamics modelling process - main stages and activities (Videira et al, 2016)

An initial step in building a participatory SD model is to synthesise qualitative impressions from the stakeholders about problem trends over time, and hopes and fears for the future. This qualitative impression is generally in graphical form, and is called a reference mode (107 p.90). Reference modes show trends such as exponential increase or decay, S-shaped growth, and oscillations (176). They may also illustrate possible future trends after a policy is carried out (176). Formulating the reference mode is an important part of the problem 'conceptualisation' stage of SD modelling (176). Reference modes can be referred to throughout the modelling process (107), as well as being useful for checking model plausibility (176). In the interviews I asked questions about AMR trends over time and best and worst case scenario projections to help develop a reference mode for AMR in New Zealand.

5.2 Model explanations

In this section I describe what causal loop diagrams are and how to read them. Development of causal loop diagrams that synthesise feedback loops involved in AMR in New Zealand was a key goal of this research. I also discuss cognitive mapping, which was an intermediary step in the development of the CLDs. The fundamental principle of system dynamics (SD) is that the structure of a system gives rise to its behaviour over time (107, 177). Key concepts involved in SD modelling are feedback processes, stocks, flows, time delays and non-linearities, which together determine the dynamics of a system (107). Feedback loops are chains of cause and effect relationships that link into loops (142), and are recognised as the main source of complexity and determinants of dynamics in a system (107, 150). These feedbacks may be positive (self-reinforcing loops) or negative (self-correcting/balancing loops) (107). In this research, the ultimate product is a causal loop diagram (CLD) model that displays such feedbacks.

5.2.1 Causal loop diagrams

CLDs are a commonly used starting point in the system dynamics tradition (136, 158) for qualitatively representing the causal structure of a dynamic system (178). They are based on system dynamics principles and are widely used for systems visualisation and communication (141). CLDs are useful for helping groups of people come to a common understanding of an issue, by incorporating a variety of perspectives on how elements of a problem are related to each other (136). Causal loop diagrams are developed by eliciting and representing people's mental models about how one thing causes another, and the nature of these relationships (136). Feedback loops between variables can then be sought (136, 177, 179). Causal loop diagrams can later be converted into quantitative system dynamics models called stock and flow models, with equations used to describe the relationships between variables. The quantitative and simulation aspects are beyond the scope of this thesis.

Causal loop diagrams (CLDs) are widely used in system dynamics. Such diagrams can be used to represent a set of causal assumptions, and are a valuable communication tool that can then be discussed and debated with stakeholders to develop a shared understanding of issues (177). Causal loop diagrams aim to show the key aspects of feedback structure that drive system behaviour (180). CLDs consist of variables

connected by arrows, which represent causal links. The arrows have polarities associated with them (+ or – signs) to indicate the type of relationship. A positive sign means that a change in the independent variable causes a change in the dependent variable in the same direction, whilst a negative sign represents that changes occur in the opposite direction (178). Variables are connected in loops that form circles of cause and effect. Small parallel lines (delay marks) may be added to arrows (see Figure 5.2) to represent links that have significant time delays.

The interplay and relative strength of different loops in a system will drive its behaviour (107). If we can identify these, there is potential to be able to take action to produce a desired result while avoiding unintended consequences. Positive (reinforcing) loops reinforce or amplify a process such that a change in any element involved in the loop will cause a cascade of changes that result in the original element changing even further in the same direction (107, 142). Reinforcing loops have the potential to generate exponential (runaway) growth in a system (142). In contrast, negative (balancing) loops counteract and oppose change (107), and tend to regulate growth (142). Reinforcing loops have either an even number of (-) arrows, or only (+) relationships. Balancing loops contain an odd number of (-) relationships (181). Figure 5.2 shows a simple example of a reinforcing and balancing loop (181).

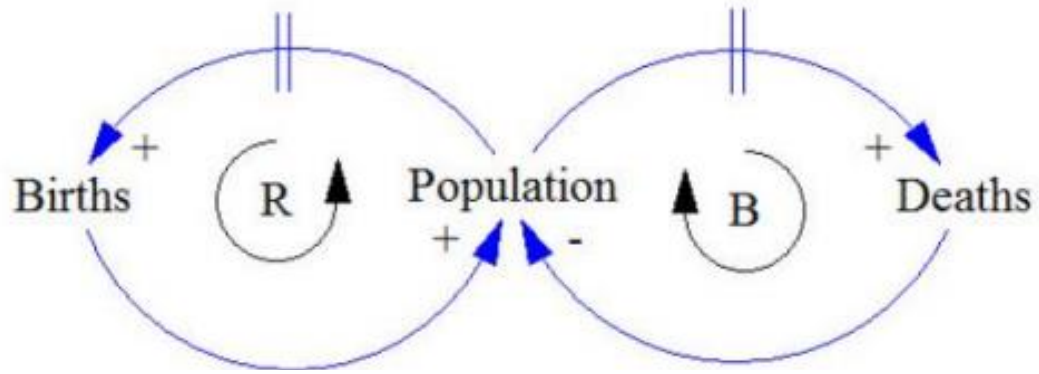

Figure 5.2 Simple example of reinforcing and balancing loops (de Pinho, 2015)

This example shows that as population size increases, eventually this will increase the number of births, further adding to the population (reinforcing loop, R). A reinforcing loop operating on its own could lead to exponential growth in the size of the population. However, as population increases, this eventually results in an increased number of deaths, limiting population size (balancing loop, B). The balance of these loops (and probably others) will determine the size of the population.

CLDs are useful for representing feedbacks and interdependencies, but a limitation is that they do not represent the stock and flow structure of systems (107). Stocks are accumulations (such as the quantity of water in a bath-tub) with inflows and outflows, and are fundamental to generating the dynamic behaviour of a system (107). Further steps in an SD modelling process would convert CLDs into a stock and flow format to allow quantitative modelling.

5.2.2 Cognitive maps

An intermediary step in developing these causal loop diagrams was drawing cognitive maps from each interview. Cognitive maps represent a person's thinking about a problem or issue, and consist of nodes linked by arrows that imply causality (182). Cognitive maps can be described as 'mental models'. Cognitive mapping is a formal modelling technique that is usually applied during interviews (182), that can be used as a basis for problem structuring to build a system dynamics model (179). These diagrams portray how people make sense of a problem, displaying their understanding of how a situation has developed and why it is problematic (179). It therefore is informed by the values and beliefs of the problem structurer (179). Cognitive maps may directly or indirectly imply an understanding of what can or cannot be done to address the problem (179).

Cognitive mapping is a useful tool for acknowledging the richness and complexity of multiple perspectives, and for identifying feedback loops (179). Such causal maps help show the causes and consequences of ideas or actions, and making sense of complex problems with a large number of ideas and interconnections (183). The direction of arrows in cognitive maps implies believed causality – the statement at the tail of an arrow is thought to influence, or cause, the statement at the arrowhead (182). Concepts are linked and related to each other to form a hierarchy of means and ends (184). Where possible, contrasting poles are included for a concept (bipolar constructs) (179).

5.3 Stakeholder selection and recruitment process

Robinson (2014) has proposed four useful theoretical and practical concerns for qualitative sampling. These are shown in Table 5.1 and were used to support my sampling procedure.

Table 5.1 Theoretical and practical concerns for sampling in qualitative research (Robinson, 2014)

	Name	Definition	Key decisional issues
Point 1	Define a sample universe	Establish a sample universe, specifically by way of a set of inclusion and/or exclusion criteria	Homogeneity vs. heterogeneity, inclusion and exclusion criteria
Point 2	Decide on a sample size	Choose a sample size or sample size range, by taking into account what is ideal *and* what is practical	Idiographic (small) vs. nomothetic (large)
Point 3	Devise a sample strategy	Select a purposive sampling strategy to specify categories of person to be included in the sample	Stratified, cell, quota, theoretical strategies
Point 4	Source the sample	Recruit participants from the target population	Incentives vs no incentives, snowball sampling varieties, advertising

To define the sample universe, we established inclusion criteria for the study. To be considered for inclusion, people had to be an expert in human, animal and/or environmental health with respect to AMR, and be in a position to understand and/or influence policy. Their work had to have a strong focus on AMR. These fairly broad inclusion criteria allowed for heterogeneity in the sample universe, which helps ensure findings are more widely generalisable (185). This is desirable for development of a shared causal theory.

There is no definitive guidance on the optimal group size for participatory modelling (104). However, it is clear there are situation dependent trade-offs that must be made (186): increased number and diversity of participants may increase the usefulness of the resulting model (187), yet on the other hand, larger groups can result in reduced communication between participants and increased likelihood of a few people dominating the conversation (188, 189), especially if there are conflicting interests (187). Richardson and Andersen (1995) prefer a group size of 12, though up to 25 is possible. Van den Belt (2004) prefers involvement of 20-30 participants. A minimum of 5-10 participants has been recommended to allow for creativity and a broad knowledge base (104). A sample range of 20-30 people was chosen for this study. This number recognised

the wide range of important perspectives that an issue as complex as AMR is likely to generate, whilst accounting for the time and resource constraints of this Masters project.

A purposive sampling strategy was chosen to identify potential people to invite to take part. A non-random approach to sampling ensures particular types of people with unique or important perspectives can be represented in the sample. Based on our understanding of the range of actors involved in or affected by AMR, we developed an *a-priori* sampling framework that would target the dimensions of human, animal and environmental health. These are addressed by different types of stakeholders (academic/research, policy, community, industry and clinical) (Table 5.2). A similar Kaupapa Māori project about AMR is operating in parallel, so specific Māori representation was not a requirement for this project. The parallel project is led by a Māori Masters student and their supervisors.

Table 5.2 A-priori sampling framework

	Human	Animal	Environment
Academic/Research			
Policy			
Community			
Industry			
Clinical			

Some of the cells in the above sampling framework have multiple important sub-areas which were already well known. Hence it was expected that participation in the project would be skewed towards some of these cells (such as human clinical). For other cells, it was expected that it could be difficult to find a suitable representative. There was some debate about whether to include industry groups in the process, as within current economic and legislative environments, the job of business is to maximise stakeholder returns. This can often be incommensurate with public health goals (190). However, we decided industry would be likely to have important insights into the issue that would be valuable to include, at least at this initial stage of the participatory modelling process. Also, the aim of the qualitative model is initially to represent a variety of stakeholder's views/understandings of AMR, including areas of disagreement.

Initial ideas for particular individuals or groups to approach came from supervisory knowledge of those in the field, asking others knowledgeable about AMR, and from looking at the list of organisations involved in the AMR working group. This is a multidisciplinary group that gave a good indication of the types of experts active in AMR policy. We also considered ideas for more 'non-traditional' stakeholders who could be valuable to talk to from the Canadian system dynamics modelling paper described in the systematised review (90). This process generated an initial list of groups/individuals to approach.

To source the sample, emails of invitation were sent out to the individuals/organisations previously identified. Where I was uncertain who was most appropriate to contact, query emails or phone calls to people in the organisation who seemed likely to know helped start the process. In some cases snowball sampling aided recruitment (chain sampling); people I approached sometimes referred me to others who would be better placed to help. I also specifically asked people I interviewed for recommendations of who else would be good to talk to. These 'referral chains' (185) helped find more participants and also to confirm that the people I interviewed were considered by others to be important to talk to. In one case I used an advertising approach to recruit – after being in contact with several environmental organisations and not finding any working on AMR, I put a small advertisement in the newsletter of an umbrella environmental group.

Potential participants were sent an email and information sheet describing the study and asking them to consider taking part. If there was no response within 1-2 weeks, a follow up email was sent or a phone call made. If interest was expressed, a consent form was sent for their consideration. If they were happy with the consent form, I liaised with them to organise an in-person interview. Copies of the information sheet and consent form are in Appendix C and D.

5.4 Data collection process

5.4.1 Semi-structured interviews

Face to face interviews were arranged at a time and place convenient for the participants. In some cases, I arranged to interview two people at the same, where they were from the

same organisation and/or expressed a preference to be interviewed together. To begin the in-depth semi-structured interviews (191) I re-iterated the purpose of the study and participants completed the consent form. I also requested permission to audio-record the interviews for the purposes of transcribing. Semi-structured interviews allow a focus on key questions with the opportunity to discuss particular areas of interest – they give the interviewer the option to explore answers in more depth (192), which is ideal for drawing out interviewee mental models and developing cognitive maps.

The focus of the interview was to explore interviewee's ideas about the main causes and effects of AMR in New Zealand, to support the development of the CLDs. Therefore, the main questions were about interviewee's opinions on the main causes and effects of AMR. During each interview I used a pencil and paper to draw out suggested relationships between variables interviewees discussed. A range of prompting questions were designed to support the development of the maps. If long 'lists' of ideas were offered, these were noted down and returned to in more detail one by one (as recommended by Bryson *et al.*, 2004). Proximal and distal drivers and consequences were explored with the aid of prompting questions such as 'what might be driving/underlying/causing that?' and 'what might be the effect/consequence/result of that?' and 'how might that relate to…?' This can be described as *"laddering up and down the chains of argument"* (183 p.187). A copy of the semi-structured interview sheet can be found in Appendix E. I tried to avoid leading questions that would prompt the interviewees to talk about particular themes, as it is preferable that they spontaneously discuss their ideas. During the interview I took notes and drew preliminary cognitive maps. These cognitive maps were then completed in more detail upon transcribing the interviews.

Other specific questions were asked to build rapport and understanding of stakeholder roles, develop an understanding of participant perceptions of AMR trends, and to specifically target questions of equity. These questions were:

1. How their job relates to AMR.
2. Why they think AMR is important/why they are interested in it.
3. AMR trends – how they think it has changed over time, e.g. linear/exponential (to help with building the reference mode).

4. Projections for future trends: what might happen if we continue business as usual, or without good policy intervention, versus what could be the best we could hope for if effective action is taken to tackle the problem (fears and hopes). These questions also helped add to the reference mode.
5. How equity issues might be involved in the issue of AMR.
6. Top policy (or high-level actions) recommendations to reduce AMR in New Zealand.

5.5 Data analysis process

Thematic analysis and development of causal loop diagrams (via the cognitive mapping step) proceeded simultaneously. Thematic analysis is a method for identifying, analysing and reporting patterns (themes) within data (193). It is important to make clear the methods used for thematic analysis, and the assumptions that informed the analysis (193). Thematic analysis was a recursive and iterative process, which was informed by the process of cognitive mapping. Identification of themes is an active process (193), and in this case coding was directed by searching for ideas about determinants and effects of antimicrobial resistance. I did not focus on the exact number of times a theme was discussed, as this does not necessarily reflect its importance (193). The aim was to synthesise a rich account of the entire dataset rather than to elaborate on very detailed aspects of a particular theme. I carried out a targeted deductive thematic analysis by searching for instances where causes and consequences of AMR were discussed. The process of thematic analysis followed the six steps outlined by Braun and Clarke (2006): familiarizing yourself with your data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report.

Listening to the audio recordings and transcribing the interviews was an important first step in familiarizing myself with the data. All the interviews were transcribed ‘intelligent verbatim’ so ums, ahs, repetitions and false starts were removed, except in cases where they indicated genuine uncertainty or hesitancy, as full verbatim would not add value for the purposes of SD modelling and thematic analysis. Transcribing assistance was provided for some of the interviews by a research assistant and a transcription company (approved by the Ethics Committee). I double checked all transcripts for accuracy and consistency of formatting and style, by re-listening to the audio while reading the draft

transcript and adjusting as appropriate. Completed transcripts were emailed to the interviewees for optional checking and approval. No response after two weeks of sending the transcripts was taken as approval. Listening to and transcribing the interviews helped me to start thinking about patterns and interesting aspects of the data.

Generating initial codes was pursued through the process of drawing complete cognitive maps for each interview. During the interviews and when finalising the cognitive maps, I had to make decisions about when to start a new cognitive mapping section or page. These decisions therefore represented a first step in the thematic analysis. Completed cognitive maps were sent to interviewees to review. This gave them the opportunity to check their ideas were represented accurately, and to make clarifications/additions. Once all cognitive maps were completed and approved, initial ideas of codes were further clarified by labelling maps or parts of maps as different types of causes and effects of AMR. For example: 'pharmaceutical economics and antibiotic development' and 'chemical co-selection for resistance' and 'drivers of prescription in humans'.

The next stage identified by Braun and Clarke (2006) in the process of thematic analysis is 'searching for themes.' Following discussion with the project supervisory team and consideration of the codes identified from the interviews, five overarching themes relating to participants ideas about the causes and effects of AMR in New Zealand were identified. The codes were organised as sub-themes under these headings. During stage four, 'reviewing themes', I re-organised some of the sub-themes as I reflected on how they would best fit together. NVivo 11 (a computer program for qualitative analysis)[4] was used to help collate the cognitive mapping diagrams from the interviews and to track sub-themes.

Stage five of 'naming and defining themes' involved further work to better name and define each theme and the subthemes within it. Stage six 'producing the report' can also be considered part of the process of thematic analysis, as I revised my ideas about what

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was most important to include. The process of writing helped to further clarify and order subthemes.

5.5.1 Development of the CLDs

Following refinement of the themes and subthemes, I was ready to develop causal loop diagrams based on the thematic analysis and the cognitive maps. The CLDs were drawn using Vensim PLE computer software (194). Vensim is a recommended package for system dynamics (180). I considered all the relevant cognitive maps associated with each subtheme and focused on identifying feedback loops. This included loops that individual interviewees identified, as well as connecting ideas from different interviewees to form loops. The nature of each loop (balancing or reinforcing) was identified by working hypothetically around the variables involved in the loop to establish how a change in an initial variable would feedback to influence itself. Preliminary CLDs were constructed for all subthemes that had feedbacks identified. Discussion and reflection with the supervisory team helped to refine and clarify the feedback loops, as well as confirming the logic and cohesion of the loops.

In cases where we postulated links that were likely to play a role based on our shared understanding of both AMR and system dynamics modelling, but were not specifically proposed in the interviews, causal arrows are shown in red. Consideration of the feedback loops identified in the literature review also helped to add detail; in cases where loops from the literature review were not reflected in the interviews, the arrows are green. In summary, the development of the CLDs triangulated the cognitive maps from the interviews, ideas from my background reading and understandings about AMR, what was learnt from the literature review, and the AMR and system dynamics expertise of the supervisors. The final step was combining the CLDs for the separate subtheme into an overall model that showed connections between the themes.

5.6 Assessing validity

As discussed in the literature review model, assessing the validity of a system dynamics model is a continual process of building confidence in the structure and utility of the model. Given that the CLDs developed here are a preliminary qualitative model, no formal quantitative validity tests were undertaken at this stage. However, transparency

about the model was ensured by giving participants the opportunity to check their interview transcripts and to approve the cognitive maps drawn from them. This helped to ensure that their main ideas about AMR were represented accurately. Working through the model with the supervision team also helped confirm the logic of the feedback loops, further building confidence in the accuracy and usefulness of the models. The model was also triangulated with previous system dynamics modelling efforts identified in the literature review.

5.7 Ethics

Ethics approval for this project was obtained from the University of Otago Human Ethics Committee (Category B) prior to commencing recruitment. No financial incentives were offered for participation in the research, unless the nature of the interviewees' job meant they required payment for their time. A small food gift was offered as thanks after the interview. Care was taken to avoid disclosing interviewee identities unless they had consented to being named in the research. In the consent form interviewees were given the option of being acknowledged as a named individual contributor, having their organisation listed as a contributor, or neither, in any written reporting. When using quotes in this thesis, care has been taken to minimise the likelihood of attribution to individuals.

5.8 Summary

This chapter has described the methods for participatory system dynamics modelling and outlined the process involved for this research. I have described the selection of stakeholders, interview process, and data analysis steps in the thematic analysis and causal loop diagram development. The next two chapters describe the results of this research. In Chapter Six I describe the participants who participated in the interviews, and discuss the results of the thematic analysis. Chapter Seven describes the reference mode developed from the interviews, and the CLDs that arose from the model building process.

6 Results: Interviews and thematic analysis

The previous chapters have outlined the reasons for choosing a participatory system dynamics approach to address AMR, and detailed the methods used to achieve this. In this first results chapter, I outline the characteristics of the participants who participated in the research, then describe the main themes and subthemes that were synthesised from the thematic analysis.

6.1 Interviewees

Thirty-one people participated in in-depth, semi-structured interviews. In four instances two people were interviewed together, making a total of 27 interviews. Twenty-six interviews were conducted in person, and one via Skype (due to time and resource constraints). Interviewees were experts in AMR or their job roles meant they had important insights into the issue. Table 6.1 shows the types of job roles or organisations they came from, and how they fit into the sampling frame. Italics have been used to indicate when participants also had a second area of expertise relevant to AMR. For example, the Infectious Disease Physician was contacted primarily for their clinical view of the problem, but they also had a strong research background on the subject (and therefore are included in italics in the research box of the sampling frame). The interviewees held a broad range of expertise across human and animal health and environment sectors. Most interviews were about an hour in length, but ranged from approximately 30 to 90 minutes.

Table 6.1 General job roles or organisations of interviewees

	Human	**Animal**	**Environment**
Academic/research	-Microbiologist, Institute of Environmental Science and Research -Clinical microbiologist *-Clinical director, microbiology* *-Infectious Disease physician*	-Veterinary academic -Veterinary epidemiologist (Epi-Insight)	-Pharmacist with interest in environmental fate of antibiotics -Ecologist -Landcare Research, systematics -Microbial geneticist *-Horticulture (Market Access Solutionz)*
Policy	-Ministry of Health -PHARMAC	-Ministry for Primary Industries -New Zealand Veterinary Association *-Rural vet (livestock)*	-Politician
Community	-Consumer advisor	*Federated Farmers*	
Industry	-Medicines New Zealand -Pharmaceutical company[5]	-New Zealand Association for Animal Health and Crop Protection (AGCARM) -Poultry Industry Association -Federated Farmers *-Veterinary epidemiologist*	-Horticulture (Market Access Solutionz) *-New Zealand Association for Animal Health and Crop Protection (AGCARM)*
Clinical	-Infection Prevention and Control nurse -Infectious Disease Physician -General Practitioner -Antimicrobial pharmacist -Clinical director, microbiology *-Clinical microbiologist* *-Pharmacist with interest in environmental fate of antibiotics*	-Rural vet (livestock) *-New Zealand Veterinary Association* *-Poultry Industry Association* *-New Zealand Association for Animal Health and Crop Protection (AGCARM)*	-Wildlife vet

[5] (Note the thoughts and opinions are of Brittany Gulledge and not representative of GSK as an organisation)

The distribution of participants was skewed towards certain boxes of the sampling frame, such as 'human clinical'. There are many different clinical roles relevant to AMR, and it was important that the included participants reflected this. The environment dimension is weighted towards academics because it was difficult to find participants who represented other role types. We were unable to find a community environmental group that was involved in creating AMR policy or advocating on environmental aspects of AMR. Several of the interviewees held senior leadership positions within their organisations, and many are involved in the AMR Action Group (an inter-disciplinary group that has designed New Zealand's Action Plan on AMR). In this sense they are in a strong position to influence AMR policy. When quotes from the interview are used for illustration in the thematic analysis, the interview number and main job role are given (P = policy, A = academia, CL = clinical, CO = community, I = industry). This is to be transparent about ensuring a wide variety of voices are represented by the quotes.

The names and organisations of those involved are listed in the acknowledgments. Twenty-five people gave consent for their names to be acknowledged, and six preferred to have only their organisation listed.

6.2 Results of the thematic analysis

The cognitive mapping process resulted in 114 A3 pages of cognitive maps, with between two and 10 pages of maps associated with each interview. It should be noted that the number of maps on each page varied depending on how extensively an idea was talked about (and therefore how much space a map occupied). Examples of some cognitive maps from the interviews, alongside more detail about how to read them, can be found in Appendix B. The cognitive maps were classified and coded into 19 subthemes. These were grouped into five overarching themes that captured the main areas of discussion regarding causes and effects of AMR. The themes and subthemes are listed in Table 6.2.

The following section comprises a qualitative thematic analysis of the interviews. I will discuss each of the themes and subthemes in more detail.

Table 6.2 Themes and subthemes from the interviews

THEMES	SUBTHEMES
1. Political and economic aspects of AMR	Pharmaceutical economics and antibiotic development
	The politics of collaboration
	Political prioritisation and funding
	International influences
2. Antibiotic use and resistance in food producing animals	Drivers and impacts of antibiotic use in food producing animals
	Industry influence, public pressure and political will
	Transmission of AMR between food animals and humans
3. Factors that increase the risk of infection and transmission of AMR in the community	Structural inequities increase vulnerability to infection
	Individual characteristics that increase vulnerability
	Factors driving AMR transmission in the community
	Companion animals
4. Antibiotic stewardship and transmission of AMR in health and care settings	Drivers of antibiotic prescription, and factors affecting stewardship
	Emergence and transmission of AMR in health and care settings
	Patient use of antibiotics 'as prescribed'
	Unintended consequences of antibiotic use in humans
5. AMR and the environment	Sources of antibiotics and resistant bacteria in the environment
	Water quality and AMR
	Chemical co-selection of antibiotic resistance
	Wildlife and AMR

6.3 Theme 1: Political and economic aspects of AMR

Antimicrobial resistance is a complex political, economic and social issue, rather than just a biomedical problem that can be addressed with traditional siloed thinking. Participants described many high-level factors that contribute to AMR, which I have divided into four subthemes: pharmaceutical company economics and development of

antibiotics, the politics of collaboration, political prioritisation and funding, and international influences.

6.3.1 Pharmaceutical economics and antibiotic development

The profit-based economic model of pharmaceutical companies was frequently identified as a barrier to the development of new antibiotics, which was seen to reduce our ability to cope with antibiotic resistance. This problem was particularly tied to the model of market-based antibiotic development, which creates a requirement for profitability:

> *"Most antibiotics are subsidised and cheap, you only pay a few dollars for them and so from a purely financial point of view from a pharmaceutical company it doesn't make a lot of sense to go to considerable effort…developing any new drug is like millions of dollars... If they're not making that commercial pay off, I mean that's just a business decision."* (A19)

One interviewee linked this situation of a market-based system of antibiotic development to wider problematic privatisation of public goods:

> *"I don't think it's an accident that antibiotics have lived the zenith of their existence also during a time when the market and our ideological belief in market forces and privatisation of public goods has also reached its zenith of time."* (A23)

Many interviewees emphasised that research and development for any drug is time consuming and expensive: it can take 12 years to bring a drug to market, and the cost to develop a new drug now exceeds $2.5 billion USD. Approximately one in 6000 products will make it all the way through the development pipeline. Research and development (R&D) is becoming increasingly expensive, including for antibiotics, because there is saturation of drug targets and mechanisms of action: *"all the low hanging fruit has been picked"* (I21). It was felt by some that the cost, difficulty and importance of innovation is not recognised enough. Other people talked about how it is much more profitable to create drugs for chronic medical conditions, where people take the medicine every day for a long time, or for illnesses such as cancer which require very expensive treatments.

Antibiotics are relatively inexpensive to buy, which reduces profit margins for pharmaceutical companies.

Several system-level perverse economic incentives were identified. Some interviewees talked about how industry promotion of antibiotics partly determines how much antibiotics are used. Most antibiotics are given a patent, so the company has a temporary monopoly on the drug which it needs to use to recoup investment and maximise returns. According to some interviewees, this has resulted in pharmaceutical companies creating demand for antibiotics in a variety of settings, including agriculture. However, as AMR emerges, it becomes less viable for industry to promote antibiotics. This is partly because over-use undermines the longevity of the product, and partly because some pharmaceutical companies may feel a sense of global responsibility to prevent AMR from worsening, and be concerned about their reputation if they were to push prescribing. Another point of interest raised was that drug companies generally educate patients and physicians about disease states to promote use of their products (including education on correct use). However, there is less incentive for providing education when it is unlikely to improve company bottom lines.

A few interviewees also thought that low access to innovative medicines is a problem in New Zealand that may affect our ability to deal with antibiotic resistance. Some said there is a waiting list of products that have been recommended for funding, with products on the waiting list for on average 3.7 years, and sometimes for up to 10 years. However, some interviewees cautioned that attributing our growing problem with resistant microbes only to shortcomings in supply may be problematic – even with more antibiotic discovery, we will be unable to deal with resistance effectively unless we do more to conserve the effectiveness of the antibiotics we already have.

6.3.2 The politics of collaboration

Collaboration between groups and disciplines was frequently discussed as a contributing factor to how well we can address AMR. Many interviewees recognised the complex and interconnected nature of AMR, and the need for a One Health approach that integrates human, animal and environment disciplines in practice and policy. However, siloed thinking was seen to be a problem both between and within disciplines:

> *"Everyone wants to do good stuff but they don't want to do it with anyone else… We're all doing individual great stuff and not sharing ... Not like the bacteria, we don't share good ideas. They share weapons and advantages, we don't."* (CL8)

The level of collaboration was also thought to affect political will to act on AMR.

It seemed many groups felt blamed or attacked by others, which stalls progress and action. An interviewee discussed how blaming others can lead to strident calls for action: *"must do this, must do that"* (P4), which can be counterproductive and *"get people's backs up"* (P4), making them less inclined to collaborate and undermining action on AMR. These kinds of comments indicate that trust is a central issue. A number of groups held the sentiment *"if you're not round the table, you're on the menu"* (I9). That is, they felt if they were excluded from groups addressing AMR, their perspectives would not be considered. There was a comment that:

> *"There's a feeling almost that it's too much to ask for people to stop taking drugs for all their little boo boos, but hey let's pretend the problem is with cattle and farmers, so then we can just put it all on the farmers too."* (I9)

Some interviewees thought that communication and collaboration is starting to improve, for example evidenced by the multi-disciplinary AMR working group. Some interviewees from human health talked about how since having better communication with people from animal health, they now think that much of the antibiotic use in food animals may be appropriate, whereas before they just saw the statistics of large volumes and thought it must be inappropriate use. On the other hand, many interviewees thought that communication between disciplines has been limited in New Zealand:

> *"Quite a big fault, we don't do it on the health side, animal people don't do it on the animal side; communicating the information that we do have."* (P3)

6.3.3 Political prioritisation and funding

A lack of political prioritisation of AMR was frequently mentioned as being an issue in New Zealand. The AMR Action Plan was widely seen as a good first step, but with insufficient people and resources to effectively implement it:

> *"The resources to do all that work aren't there. There's no funding. So the AMR group comes up with all these actions, and it's like how are you going to pay for it?"* (I7)

A variety of factors were thought to influence the prioritisation of AMR. These included inter-related factors of public pressure, media attention and surveillance infrastructure (more infrastructure is likely to result in more surveillance 'hits'). Several interviewees thought competing issues such as *Mycoplasma bovis (M. bovis)* are being given priority. Strength of lobbying from various interest groups was also said to affect political will to act. Many interviewees felt a long-standing focus on non-communicable diseases means there is less funding available for infectious disease research. Further, ideology and party politics were said to have an important effect on how and whether an issue is addressed:

> *"Three million dollars was allocated to set up an antibiotic resistance surveillance system… but then shortly after, the National Party came into power and the money was never properly utilized. Because the idea was they were going to set up a monitoring system for antibiotic resistance across New Zealand. And so that never happened, and that was a decade or so ago."* (P6)

6.3.4 International influences

Several interviewees raised the idea that many resistant infections in New Zealand may originate overseas, and attributed rising AMR rates in New Zealand to globalisation of trade and international travel. AMR was seen as a global issue, with AMR levels in resource and regulation poor countries being a particular concern. Some interviewees argued that the main AMR threat to New Zealand is likely to originate overseas. Factors such as ease of public access to antibiotics, poor sanitation, and low environmental standards for manufacturing pharmaceuticals were thought to make Asia and other areas particular hotspots for AMR, which could have flow on effects for New Zealand. It was

thought that fewer regulations on antibiotic use in animals and increased contact between humans and animals may also contribute:

> *"…Very high-risk, particularly in that one health sphere that we sit in, that human/animal/environment interface. There's some amazing data coming out of Asia… sometimes quite scary in terms of how much antibiotics they use, unregulated. Sometimes they're using four different antibiotics in pig and poultry feed, and all that manure goes straight into the pond where they get their fish from, and people get their water from the same sources and everything…"* (CL11)

Participants discussed how globalisation means there is a huge amount of travel and trade, with international movements of people and animals. Some interviewees thought rising rates of medical tourism could increase the risk of resistant infections being introduced to New Zealand with returning patients. In the past, contact with healthcare settings overseas was the main concern, but now resistance in communities is also high, so travellers not exposed to healthcare settings are also at high risk of acquiring resistant bacteria. A few participants also considered resistance to be a potential problem in imported food from areas where animal agriculture is more intense.

6.4 Theme 2: Antibiotic use and resistance in food animals

Many interviewees discussed the use of antibiotics in food producing animals (FPAs), and whether this could pose a threat to human health. I will address AMR in FPAs separately to companion animals and wildlife, because the way humans interact with them and the way they are administered antibiotics is quite different. For example, food animals tend to be raised on large scales and high intensity, which drives herd-level treatment (often prophylactic) rather than individual treatment. In contrast, pets are prescribed antibiotics under similar rationales as humans. Interviewees drew parallels between the dilemmas companion animal vets and human doctors have regarding individual care versus considering the wider community impacts of antibiotic resistance. Therefore, companion animal prescribing is discussed in the next theme. Wildlife are mentioned in the environmental section as they were considered by participants to be part of the wider 'ecology'.

6.4.1 Drivers and impacts of antibiotic use in food animals

Interviewees held a variety of perspectives on the importance of antibiotic use in animal agriculture and what, if any, implications this may have for human health. Some felt that resistance transmission from food animals to humans is likely to contribute to a significant portion of AMR in humans, whilst others thought this transmission is practically unlikely, particularly in the New Zealand context.

Intensity of animal agriculture was seen by many interviewees as a key determinant of the level of antibiotic use in food animals. The rationale was that intensification increases the number and density of animals, with increased potential for disease transfer, resulting in increased prophylactic and overall antibiotic use. However, some disagreed, arguing that intensive farming systems allow for increased control of the animals' environment and better management of effluent, reducing spread of disease and therefore reducing the need for antibiotics. Many interviewees discussed the importance of disease prevention through hygiene, vaccination, nutrition and biosecurity measures. Some interviewees thought that industry influence is a driver of the belief that antibiotic use is necessary for animal health and welfare, and financial viability. The intensity of animal agriculture globally was seen to be driven by a demand for animal products, and in particular affordable animal products. One interviewee from human health put it this way:

> *"It's funny isn't it, because - I might be wrong - agriculture has embraced antibiotics for economic reasons, but it's going to have the opposite effect."* (CL1)

Many interviewees thought that antibiotic stewardship by farmers and vets would affect levels of AMR. Stewardship is here defined as reducing use and increasing appropriateness of charting (prescribing), including antibiotic choice, dosing and spectrum. Some people felt that vets tend to over-prescribe antibiotics, while others thought antibiotic charting by vets is generally well regulated and implemented in New Zealand. Those involved in animal agricultural industries said they took care to avoid use of antibiotics of human significance. Factors thought to influence stewardship included level of education of vets and farmers, competing issues such as *M. bovis*, cost of testing and timeliness of results, and regulations on charting (prescribing). A perverse incentive was identified with regard to nil-withhold antibiotics: there are large fines for antibiotics

found in milk, so farmers may be more likely to choose nil-withhold antibiotics for this reason, which may not be the best choice for a particular infection (therefore contributing to development of AMR).

Some people on the animal health side felt that the growing debate about use of antibiotics in animals could result in re-classification of important antibiotics. This was cause for great concern, as they felt they may lose access to some key antibiotics essential for animal health and welfare, such as penicillin. This has resulted in stronger guidelines by the Veterinary Council to promote antibiotic stewardship and leadership in this area, to ensure longevity of antibiotic effectiveness and reduce the risk of losing charting rights.

Interviewees agreed that AMR has serious impacts on animal health and welfare, increasing morbidity and mortality. Livestock with persistent infection will often be culled, which is hard on farmers economically and emotionally. Many participants believed that levels of resistance in FPAs is an important issue abroad, but less so in New Zealand. This was attributed by many to our 'relatively low' use of antibiotics in livestock, resulting from our less intensive pastoral farming systems, and a robust regulatory system for veterinary medicines. Most interviewees assumed that antibiotic resistance drives use, though some interviewees with expertise in animal health said this may not necessarily be a straightforward linear relationship:

> *"It doesn't appear that our use is triggering an increase in resistance in animals. So all of the stuff we're doing (to reduce antibiotic use in food animals) is around mitigating AMR in people."* (CL11)

Interviewees with animal expertise were generally more sceptical of animal-human transmission. On the other hand, some interviewees felt that agricultural antibiotic use is high in New Zealand, and that this could pose a threat to human health. Increasing farming intensity, including establishment of feedlots, was seen by some to increase risk of AMR. There was a perception that in New Zealand farmers are well aware of consumer desire for antibiotic-free agriculture, and respond to that, but that they aren't so concerned about resistance transmission from animals to humans:

> *"...Farmers understand there is a market desirability for low antibiotic use, for clean green, you know... healthy, welfare, all that sort of stuff - they've got that picture... I don't think I've heard anyone get wound up about the fact that 'oh if we use too many drugs that can affect human health.' I haven't heard that. It's more about the perception for marketing."*(I9)

Keeping antibiotic use low was perceived to be a defensive market issue, to maintain New Zealand's premium position.

6.4.2 Industry influence, public pressure and political will

Interviewees discussed how industry influence and public pressure may impact on the political will to act on AMR. Some interviewees felt that agricultural lobbying promotes the message that antibiotics are essential for animal health, welfare and productivity, thus driving antibiotic use in food animals. Some thought that strong agricultural influence is a barrier to political action on AMR. On the other hand, the influence of 'activist types' was seen by some as spreading the 'incorrect' idea that antibiotic use in animals is risky for human health. I was informed that voluntary actions are being taken by the agricultural industry in New Zealand to reduce antibiotic use, as precautionary measures.

Several interviewees thought that independent research is more likely to find a problem with AMR in animals compared with commercial research, which would increase public concern about AMR in animals, resulting in pressure on politicians to act to restrict antibiotic use in FPAs. A concern was raised that the influence of the agricultural industry might restrict research on AMR in food animals, through sending a *"clear message that this was not an area the industry wanted investigated"* (P6). On the other hand, those involved in food animal industries and animal health argued that these industries and vets are genuinely committed to antibiotic stewardship, and they put forward reasons for why antibiotics are used in certain ways. Further, the poultry industry funded studies themselves on resistant bacteria in chickens, through public academic institutions.

6.4.3 Transmission of AMR between food animals and humans

Another subtheme from the interviews was transmission of AMR. Many participants described the potential for transfer of AMR from animals to humans, but there was variation in how much they thought it happens and how practically important it might be for AMR levels in humans. Some participants argued there is little concrete evidence for animal to human transmission, but thought it is reasonable to reduce antibiotic use as a precaution. Several thought animal to human transmission is unlikely to be a big issue:

> *"Obviously we use a lot of antibiotics for drying off cows and things like that, but how much that flows on to contributing to AMR in humans, I'm far from convinced. We also use lower amounts in New Zealand agriculture, so I think to point the finger at the agricultural industry would be wrong... But I don't think we really have a good handle on it."* (A2)

Other interviewees thought there could be several plausible pathways of resistance transmission between food animals and humans, including direct contact (e.g. farm and abattoir workers), and via contamination of the food chain with resistant bacteria. Antibiotics and resistant bacteria entering the environment from food animals (via faeces, urine and milk) was thought to create an important reservoir of AMR that humans could then be exposed to. Use of contaminated manure as fertilizer was also considered to be a potential pathway. Some thought the evidence for direct transfer of whole organisms from animals to humans is 'sketchy' but that horizontal gene transfer from organisms in food could play a role. For example, humans may ingest animal bacteria with food, which can then mix with our gut flora and pass on resistance genes to human adapted bacteria. A number of interviewees also pointed out that resistance can go both ways - and the direction of transmission is not always immediately clear even from epidemiological studies, which could lead us to make incorrect conclusions about the source species.

6.5 Theme 3: Factors that increase the risk of infection and transmission of AMR in the community

Many participants described factors that increase people's risk, or vulnerability to, infection - and hence AMR, and discussed drivers of emergence and transmission of resistant bacteria in the community. For the purposes of this discussion, I define

‘vulnerability’ to mean susceptibility to infection and /or likelihood of being exposed to infection.

6.5.1 Structural inequities increase vulnerability to infection

Many interviewees discussed how structural inequities increase the vulnerability of certain groups in New Zealand to infection. Socioeconomic deprivation and the associated poor nutrition, low housing quality and over-crowding were considered. Some argued that New Zealand’s social welfare system is failing to empower people and they attributed high levels of inequality in New Zealand to an unfair economic system.

Several plausible but opposing effects of deprivation on antibiotic prescriptions were proposed. Some interviewees thought that physicians may be more likely to use extra caution for people they consider especially vulnerable, and therefore prescribe more to those groups. Others discussed how those on lower incomes may be more likely to have pressures of multiple jobs to juggle, bills to pay and limited sick leave. Combined with unaffordability of doctors’ visits, this may mean they delay care-seeking until their illness is severe: *“unless they really, really, really have to, they won't go (to the doctor)”* (CO16). On the one hand, accessing healthcare late may reduce the number of antibiotic prescriptions, while on the other hand, being more ill due to delayed care seeking could increase the likelihood of being prescribed antibiotics. A ‘she’ll be right’ attitude was also thought to contribute to late access to health care.

Many participants identified inequities by ethnicity as an important aspect of the AMR system. Considering that Māori and Pasifika groups are disproportionately represented in more economically deprived deciles and experience a higher burden of infectious disease (see section 2.1), some interviewees thought that antibiotic prescriptions would be higher for these vulnerable groups. However others said prescriptions are only slightly higher than average for these groups, which may represent unmet need and inadequate access to antibiotics. As well as difficulties accessing health care in terms of affordability, some interviewees felt that Māori are less likely to be prescribed antibiotics when they need them due to underlying institutional and interpersonal racism. As we move towards limiting antibiotic use, many interviewees noted that it is important to ensure equitable access is maintained (or attained):

> *"There are things we've got to be careful about as we try to address AMR, one is that as we try to reduce antimicrobial use we don't reduce access to legitimate antimicrobial use among vulnerable populations, and that is a real risk."* (CL24)

6.5.2 Individual characteristics that increase vulnerability to infection

A common topic of discussion was factors that increase an individual's likelihood of acquiring an infection that may require antibiotics. In addition to groups most affected by structural inequities, specific groups who were thought to be at increased risk of infection included the very young and the elderly, very sick patients (e.g. immunocompromised), and migrants who may have difficulties understanding and accessing the New Zealand health system. Some also said that flu vaccination reduces the chance of secondary bacterial infection and so can reduce the need for antibiotics. Good management of skin health was also seen as crucial: "*Managing eczema really well is a really important way to prevent skin infections"* (CL26).

6.5.3 Factors driving AMR transmission in the community

Interviewees discussed a variety of factors that may increase transmission of resistant infections in the community. The amount of antibiotics used in the community was considered to be very high, and a key determinant of the spread of AMR. Participants considered that the level of antibiotic use in a community will provide selective pressure for AMR growth, and is likely to facilitate establishment of resistant infections when they are introduced from overseas:

> *"Whenever they* [resistant bacteria] *emerge overseas, sooner or later they'll turn up here. Then what determines how fast the rate of exponential growth is in the prevalence of resistance to that antibiotic in that organism, is determined I think primarily by two things. One is infection control and the other is the level of antimicrobial consumption."* (CL22)

A general agreement was that the more carriers of infection (including resistant bacteria) there is, the greater the risk to other people in the community.

The same factors that delay care-seeking may also result in people going to work or sending their children to school when they are sick, which can drive transmission of infection. Additionally, lack of understanding about how infection spreads may lead people to think it is harmless to go to work, or see being sick as an opportunity to get other errands done. The invisibility of bacteria could make it harder for people to understand infection and the importance of hand hygiene, facilitating spread of illness: *"And I guess the other thing with bacteria is you can't see it."* (CL1)

Level of hygiene/sanitation was seen as a very important influence on how easily infection spreads in the community. Better sanitation reduces rates of faecal-oral transmission, limiting rates of colonisation and spread in the community. Participants felt that in New Zealand we have generally good sanitation infrastructure (e.g. water, sewerage), but this is much more of an issue in the AMR picture internationally. However, several interviewees thought New Zealand still has an embarrassing level of poverty for a 'first world' country. This is likely to create geographic areas where transmission is more common.

6.5.4 Companion animals

Several people talked about companion animals as being part of the AMR picture. I discuss companion animals in this section because they are such an integral part of humans' lives, they fit more closely with this section than others. The closeness of contact between owners and pets was seen by many interviewees as a risk for transferring resistant bacteria (in both directions). Having domesticated animals in hospitals may also pose risks in terms of transmission of resistant bacteria. The cost of culturing and antibiotic susceptibility testing was described as unaffordable for many owners, which could lead vets to have to make a best guess about whether (and which) antibiotics are most appropriate:

> *"…in clinical practice, you're constrained by finances, it's always an onus on the decision around progressing further testing etc. So you can do culture and sensitivity which is great, we should all be engaging in that …but the reality is, it has to be paid for by somebody, so if your client says, 'actually I can't*

afford to do that', you don't just not treat the cat, you go 'well, this is my best guess about what we should be doing'." (P13)

This could contribute to resistance in animals. Vets can feel a strong pressure to prescribe from owners who do not want their animals to suffer. Like in human medicine, there is a conflict between focusing on individual health versus considering wider public health consequences. Someone also discussed how pets may be exposed to chemicals such as herbicides in the neighbourhood environment and track these into the home, which may co-select for physiological resistance. Animal shelters were mentioned as potential hotspots for AMR spread. Given the number of animals living together in close proximity, infection transmission can happen quickly.

6.6 Theme 4: Antibiotic stewardship and AMR transmission in human health and care settings

This theme is about drivers of antibiotic prescription, stewardship by prescribers of antibiotics, and factors affecting whether patients use them as prescribed. There is a sub-theme about drivers of the emergence and transmission of AMR in health and care settings. There is also a section about the impacts of resistance in humans, and other unintended consequences that can result from antibiotic use. Overall human antibiotic use was thought to be driven by population size and level of antibiotic stewardship. Many people thought that AMR in humans is mainly the result of overuse of antibiotics in humans (and not very linked to use in animals). Some interviewees felt that New Zealand is lagging behind on AMR action, and expressed concern about our high use of antibiotics in humans. Most interviewees felt that antibiotic prescription in the community was more of a problem than hospital prescribing (I was told that about 95% of total antibiotic prescriptions in humans are done primary care in New Zealand) due to volume and the fact there is less opportunity to ensure compliance than in hospital. It was thought that there is a lot of over-prescribing in this area for things that are minor and trivial.

6.6.1 Drivers of antibiotic prescription, and factors affecting stewardship

Many participants talked about the myriad of pressures on GPs to prescribe antibiotics. Some felt that antibiotic prescription is now almost standard practice and that public

sentiment is: *"If I don't leave with an antibiotic the doctor hasn't done the right thing"* (I20). One person noted that *"the average New Zealand child before they go to school has 8 courses of antibiotics, which is also a world record"* (CL8). Some interviewees felt that historically lax stewardship has led to high patient expectation of receiving antibiotics. Some referred to threats from patients putting pressure on GPs to prescribe antibiotics.

Many interviewees thought that the cost of GP visits can increase patient expectation of antibiotics, and doctor's feelings of obligation to prescribe. The majority of interviewees raised the idea that consumers expect to get something for their money, and this can translate to expectation of a prescription. Doctors may feel they need to 'give value' by prescribing. Further, both doctors and patients know that follow up visits are unlikely when cost is an issue. This may make 'back-pocket' prescriptions (prescriptions with the advice to get antibiotics if a patient gets worse) more commonplace. High patient numbers and short consultation times may mean doctors aren't able to take the time to address underlying issues. Giving a pill is a quick fix – *"clinicians are treating the problem rather than the person"* (CO16). Doctors may wish to avoid conflict, and especially when under time pressure it may be easier to just write a prescription and avoid a complicated interaction.

Several interviewees discussed how prescribers, particularly GPs, are caught in a 'grey zone' where they have to balance concern for the health of individual patients with the broader public health threat of antibiotic resistance. Doctors are likely to be cognisant of wanting to fulfil patient expectations in order to ensure they don't lose patients from their practice, which would result in potential loss of self-esteem and income. They may also worry about being subject to a complaint if they don't. Further, doctors may have the attitude that 'if I don't, someone else will'. GPs are also under pressure to avoid hospital admissions, and effective use of antibiotics in primary care can help achieve that.

Some interviewees thought that prescribers and patients tend to only think about the benefits of antibiotics, and not the possible harmful side effects. They may be seen by patients as a 'miracle drug' and prescribers may have a 'prescribe just in case' attitude. Lack of patient understanding about the differences between viruses and bacteria may

also put pressure on GPs, to just give 'something'. In this way antibiotics may be used as placebo drugs to meet patient expectations.

Hospital prescribing was also discussed. Generally, hospital prescribing in New Zealand was thought to be well managed. Hospitals have access to expert advice and the ability to monitor patient adherence closely, as well as the opportunity to easily change antibiotics as a result of susceptibility testing. It was thought that the level of skill, confidence and ability to monitor patients closely in hospital means prescribers are more willing to hold off giving antibiotics or to stop antibiotics. Barriers to hospital stewardship mentioned by interviewees included an attitude of 'you don't tell doctors what to do' and a cultural hierarchy in some cases between various health professionals.

Fear was a general theme thought to drive over-prescription. People concerned for their (or their children's) health may demand antibiotics. Some interviewees thought there is quite a lot of fear amongst the public with regard to infectious diseases, due to social media, scaremongering in general media, and strong Ministry messaging around infectious diseases such as rheumatic fever and meningitis. Participants understood that New Zealand still has high rates of infectious diseases, and doctors may fear a worst case scenario if they don't give antibiotics:

> *"I think also fear drives a lot of the expectation from the public ... But I don't think that's just the public. I think there's a fear in prescribers that they'll miss something important."* (P3)

Antibiotic choice (narrow spectrum is generally preferable for limiting resistance), dose and course duration were discussed under the theme of stewardship. Limited testing availability and lack of timely, useful lab results were said to make it harder to ensure the correct antibiotic and regime is chosen. Mixed messages around prescribing and use were also thought to impair stewardship. For example, previous guidelines recommended completing antibiotic courses, while currently there are moves to encourage patients to stop taking the doses once they start to feel better – though there was some disagreement among participants about whether this is a good idea. Difficulties keeping up to date with prescribing guidelines were also mentioned.

6.6.2 Patient use of antibiotics 'as prescribed'

A number of reasons were raised as to why patients may not use antibiotics according to the prescribed recommendations, which they thought could have implications for antimicrobial resistance. Patients may stop taking antibiotics early because they feel better, or if they experience side effects. Physicians may have limited time in a consultation to discuss how the medicines should be taken. Lack of patient understanding about antibiotic resistance (in some cases linked by participants to socioeconomic deprivation) was thought to result in behaviours such as medicine hoarding and sharing. Another factor raised was that the level of rapport a physician has with a patient will affect how likely they are to follow recommendations.

It was thought that in some cases, cultural factors may influence how antibiotics are used. For example, in some countries, antibiotics do not require a prescription, which may mean people travelling to New Zealand from such countries may have elevated expectations of receiving antibiotics. An idea was raised that receptiveness of different groups to messaging about appropriate antibiotic use is influenced by how much they can relate to the content of those messages. For example, if Māori are not represented in graphics whilst other ethnicities are, Māori may be more likely to think the recommendations don't apply to them:

> *"...because they don't see themselves there. What a lot of people are going to say about those pictures – 'well they're lovely. But that's not for me'... it's actually pulling them (those designing the messages about antibiotics) back into reality. And saying that it might be nice for you, the person delivering those nice pictures..."* (CO16)

6.6.3 Emergence and transmission of AMR in health and care settings

Hospitals and rest homes were frequently identified as settings that are likely to be 'hotspots' of AMR. Reasons included high numbers of sick people in close proximity, in contexts where antibiotic use is high. Also, patient skin integrity can be compromised due to wounds and IVs and so on, further facilitating spread. People in rest homes were seen as likely to be highly vulnerable to infection for a number of reasons, including age,

severity and number of co-morbidities, and skin fragility. The need to make some decisions (e.g. use of catheters) based around ease of patient care, versus what is really necessary, may contribute. Overall these factors may result in higher antibiotic use and therefore levels of AMR in rest homes. The difficulties of not consistently having a doctor available on site was thought to reduce timeliness of prescribing, further contributing to the problem.

In hospitals, standards of infection prevention and control (IPC) were commonly discussed as a crucial way of preventing transmission of infection (including antibiotic resistant bacteria). IPC reduces the likelihood of needing antibiotics and therefore reduces AMR emergence, as well as limiting the spread of existing resistant bacteria. The distance between patients was seen as an important factor in transmission, and overcrowding in ED could be a particular risk. Building design may impact IPC - many interviewees talked about how multi-bedded rooms and sharing of toilet facilities in hospitals may increase risk of transmission. Staff movements between patients were said to increase indirect transmission of microbes between patients if hygiene procedures are not well adhered to:

> *"My ideal hospital would have a bunch of single rooms each with a toilet, and people wouldn't share… Six bedded rooms in the hospital with shared toilet facilities, those provide an opportunity for transmission. And healthcare workers can also be a vector if they're not washing their hands."* (A2)

Consistency of screening and isolation procedures was also said to be important.

Staff commitment to the use of standard precautions, such as personal protective equipment, hand hygiene and cleaning standards (including shared patient equipment), was seen as very important. Staff buy-in to IPC practices were said to be affected by education, and how simplified and streamlined policies and procedures are. Busyness may reduce compliance, as can inadequate access to facilities (e.g. for handwashing). When under time pressure, systems for IPC may start to break down. The level of rapport educators and champions of IPC have with other staff was thought to play an important role in encouraging high uptake of IPC practices.

Cleanliness of hospital facilities was frequently discussed as key to reducing transmission. Cleaning standards may be affected by level of staff training. Financial pressure on hospitals was thought to increase likelihood of contracting cleaning services out to the cheapest bidder, which may potentially compromise cleaning standards. Whilst cleanliness is important, on the other hand some interviewees discussed the paradox that some cleaning chemicals may co-select for antibiotic resistance in bacteria. Therefore, the type of cleaning chemicals used may contribute to the problem. One interviewee said that older hospitals may have less smooth surfaces and be harder to clean, resulting in more use of cleaning chemicals compared to a newer building.

Environmental factors such as building maintenance and material choices were also thought to have an effect on transmission of infection. For example, keeping up with maintenance helps to control air flows and pests, while choosing surfaces that are easy to clean (such as vinyl flooring, as opposed to carpet) improves hygiene standards.

With regard to infection transmission in rest homes, some interviewees thought that these settings may not have dedicated infection control teams, which would reduce oversight of infection prevention and control and may lower hygiene standards. This could result in staff inadvertently transferring bugs between patients, especially if rigorous cleaning procedures are not followed. The number of patients with incontinence may also increase the problem. It is also difficult to put people in isolation when a rest home is their residence, as this could be seen almost as punishment.

This theme and the previous two themes make clear a common idea held by interviewees: that having lots of animals (or groups of humans) living in close quarters is a risk factor for AMR, particularly when infection control practices are lacking.

6.6.4 Unintended consequences of antibiotic use in humans

Interviewees agreed that in humans, as a general principle, 'use drives resistance.' Participants discussed a range of impacts of antibiotic resistance. There was consensus that the more we use antibiotics (particularly inappropriate use), the more antibiotic resistance will impair our ability to prevent and treat infection, which has far reaching effects. It can take some time to realise that a treatment is not working (and why), leading

to prolongation of disease, longer periods in hospital and increased healthcare costs. Treatment failure increases risk of patient morbidity and mortality, and is particularly dangerous for immunocompromised patients and people undergoing surgery. As first line antibiotics of choice become ineffective, this can lead to use of more expensive and less desirable antibiotics, which often have worse side effects. In general, resistance was seen as an urgent threat to the provision of high-tech healthcare that Western medicine is known for. There is a conflict between wanting to optimise individual health by using antibiotics, and wanting to preserve antibiotic efficiency and minimise intergenerational inequities for this *"non-renewable resource"* (A23).

Several interviewees projected increasing isolation requirements as resistant infections rise. Whilst it was recognised that isolation is an important tool for reducing transmission, some possible harmful effects were also identified. Patients may experience psychological harm from social isolation, as well as physical harm due to delays to tests and procedures, resulting in poorer outcomes.

A small number of interviewees mentioned some other possible negative impacts of antibiotic use through disruption of an individual's microbiome. These included potential links with Type 2 diabetes, obesity, heart disease, and autoimmune conditions:

> *"One of the real issues we have is we don't see antibiotics as doing harm, we only see them as doing good. So we give them just in case because what harm could it do? But I think as our knowledge of the microbiome starts to develop, and it's really in its infancy, we'll realise we're actually causing a lot of the long term problems we pick up in all the patients."* (CL8)

6.7 Theme 5: AMR and the environment

Several interviewees saw the environment as an important but poorly understand aspect of AMR. They discussed this theme in different ways: routes by which antibiotics and resistant bacteria may enter the environment, links between AMR and water quality, and co-selection of resistance by the range of chemicals humans use in their everyday lives. Finally, wildlife are also mentioned in this section because they are commonly considered part of the 'environment'.

6.7.1 Sources of antibiotics and resistant bacteria in the environment

Interviewees discussed a range of routes through which antibiotics and resistant bacteria may enter the environment. Many participants discussed how antibiotics are excreted mostly unchanged from humans (and animals), so wastewater from residential, hospital and agricultural sources may contain these contaminants. Livestock farming was often identified as a key source of antibiotics entering the environment. Some interviewees thought we use large volumes of antibiotics in food animals in New Zealand, and discussed how animal effluent goes directly onto the fields, and may then enter the groundwater or runoff into waterways.

New Zealand does not currently have waste water treatment systems that can remove pharmaceuticals, so they may eventually end up in waterways and the ocean. Incorrect disposal of antibiotics may also contribute (e.g. flushing down the toilet):

> *"So, the theory is to bring it* [unused antibiotics] *back to the pharmacy and the pharmacy is supposed to work out how it needs to be taken care of. But it's a bit haphazard how that happens."* (A12)

Depending on the robustness of the disposal systems (e.g. incineration is better than landfill, lined landfills are safer than leaching), antibiotics may also enter the environment through that route. Internationally, discharge of antibiotics from pharmaceutical manufacturing factories (especially where environmental standards are lacking) into waterways was thought to be a problem, as it results in antibiotic concentrations that are sub-lethal to bacteria.

Overall, increased levels of AMR in environmental bacteria were thought to increase the risk of transfer of resistance genes to human pathogens. It was thought that antibiotic characteristics such persistence and potency will affect how long antibiotics remain in the environment, and the level of selection pressure exerted on environmental bacteria. It is possible that crops may be contaminated with antibiotics or resistant bacteria, or they may reach drinking water systems. People can also be exposed through activities like swimming and food harvesting in contaminated waters.

Some interviewees thought horticultural use of antibiotics could be an issue, especially at times when bacterial disease in crops are high. For example, *Pseudomonas syringae pv. actinidiae* (Psa) is a bacteria that affects kiwifruit. It was thought that problems such as this might result in more off-label use of antibiotics by growers. However, others talked about how New Zealand has auditing and certification processes that encourage growers to keep to recommended spray regimes. Evidence of residues would also have a significant impact on industry reputation. One interviewee said that growers do not view AMR specifically as a threat, but the concept of resistance in general (e.g. to insecticides/herbicides) is.

6.7.2 Water quality and AMR

Several interviewees made strong connections between water quality and AMR. Concern was expressed about waterways as a reservoir of AMR. Farming practices and entry of livestock manure into groundwater and streams was especially concerning. Waterways could then be a source of exposure of AMR to other animals and to humans. Contamination of water with other chemicals such as herbicides and pesticides was also seen to create conditions for resistance emergence.

An interviewee discussed how as population size and density increases, more sophisticated water treatment systems are required. Some participants argued that in some areas of New Zealand, urban growth has been unmatched by wastewater treatment infrastructure. Release of urban and rural wastewater into our waterways was said to severely affect water quality. There were suggestions that the level of contamination of rural waterways could be related to intensity of animal agriculture and the amount of chemicals used in horticulture. Complacency about water quality was seen to be an issue:

> *"We do have an abundance of water so we're a little bit arrogant about not being as good as we can for keeping it clean. Or understanding its potential influence on us."* (A14)

6.7.3 Chemical co-selection of antibiotic resistance

Some interviewees discussed how when bacteria are exposed to certain chemicals, this increases vulnerability to changes in their genome, including triggering of resistance genes:

> *"I think the more stressed an organism is, the more likely it is going to respond to pressures … the more pressures they're under, the more chemicals that are attacking their cell walls, coming through their pores, the more vulnerable they are to stuff happening to their genome."* (A14)

I was told that resistance genes are continuously being cycled by horizontal gene transfer, but will only accumulate in a population if there is a selective value to that gene. Participants discussed a wide variety of chemicals that may co-select for resistance genes, ranging from herbicides, pesticides and cleaners to personal care products. For example, one interviewee described how herbicides (which are heavily used in both agricultural and urban environments) may accelerate the evolution of antibiotic resistance 100,000 times faster than if there was absence of herbicides. This may be a physiological resistance that is temporary, that reverses when the stressor is removed. Some interviewees thought that we seem to have become very complacent about commercial cleaners, not considering their harmful potential. Over-use of antibacterial products may be fed by a fear of germs, which could be a result of both sensible public health knowledge, and industry advertising of cleaning products.

6.7.4 Wildlife and AMR

AMR in wildlife was rarely discussed. One participant mentioned that migratory birds could possibly carry resistance genes and transmit them to humans. However, this was an area of high uncertainty as to whether it is practically likely to pose a significant threat to humans. I was unable to interview anyone who was an expert in AMR in wildlife, but did gain some understanding of zoo animals and AMR. AMR was not considered to currently be a big issue in zoo animals, although there was certainly an awareness of the issue. The way zoo animals are administered antibiotics is similar to humans and pets in that it is focused on the individual rather than herd treatment. Zoos generally try to avoid having to give animals antibiotics, so there is a focus on prevention of infection:

> *"…Good diet, good nutrition, good environment, not a stressful environment, no overcrowding - all these are things that we can control in the zoo…"* (CL27)

Lack of pharmacological studies in wildlife means drugs aren't very well tested. Also, doing diagnostic tests can be difficult on wild animals. Antibiotic choice for zoo animals depends on a variety of things, not just sensitivity results, such as which antibiotics are most feasible to administer to a wild animal.

6.8 Summary

This chapter has described the range of stakeholders who took part in interviews, and discussed the key themes and subthemes resulting from a thematic analysis of the interviews. Five major themes relating to causes and effects of AMR were identified: political and economic aspects of AMR; AMR in food producing animals; human vulnerability to infection and transmission of infection; antibiotic stewardship and use; and AMR and the environment. The next chapter comprises a second results chapter. It describes causal loop diagrams that were developed for some of the subthemes discussed in this chapter.

7 Causal loop diagram analysis

The previous chapter outlined the results of a targeted thematic analysis exploring interviewee's ideas about the causes and effects of AMR. This chapter begins by outlining the reference mode. Then the main focus is describing the causal loop diagrams (CLDs), which were synthesised from the interview thematic analysis, the cognitive maps, the literature review, and the expert knowledge of the research team. The CLDs consist of endogenous variables (involved in the feedback loops of the system (176)), and exogenous variables, which are not directly involved in the loops. The exogenous variables were described in the thematic analysis, so whilst they are included in the CLDs diagrams they are not discussed again here. Larger versions of the CLDs with exogenous variables included (where applicable) are available in Appendix F. Please see the separate booklet (Appendix G) submitted with the thesis for larger versions of the causal loop diagrams in this chapter (with exogenous variables excluded).

7.1 Reference mode

The reference mode (see section 5.1) for this study is a qualitative graphical impression of how the interviewees believe AMR has changed over time, and their hopes and fears for the future. Interviewees all agreed that AMR levels have been increasing over time, but had varied ideas about the pattern of growth. Some were hesitant to comment on a pattern, citing limited data and changing surveillance methods. Several thought AMR has been increasing exponentially, and noted this may not be evident when resistance levels are low, but could result in sudden dramatic increases. Some thought the rise was linear, and a few thought step wise increases over time were likely. Some interviewees discussed the possibility of a sigmoid curve where resistance rises exponentially before levelling off. Several interviewees noted that the pattern would be different for different microbes, or said that there could be a range of patterns over time. Rising levels of resistance in gram negative bacteria was seen as particularly concerning. A few interviewees mentioned that the problem of resistance could be slightly over-estimated.

Many interviewees thought the best possible scenario would be to slow the rate of increase in AMR. Some hoped that with enough effective action, we may see a plateau in resistance levels. Several agreed the best we can hope for is to be able to manage the

situation by ‘buying time’; slowing the transmission of AMR for long enough to allow development of new effective antibiotics. The optimal situation, some said, would be to keep functioning antibiotics for almost every infection. Some worried that we may have passed the point of being able to get the problem under control.

Figure 7.1 displays the ideas above as a graph. The trend until now is simply described as increasing, depicted by a linear line, due to the variety of ideas about the exact pattern of increase. The worst fear participants had was that AMR would increase exponentially from now, as a runaway growth pattern. The most optimistic ‘best case’ scenario that was put forward was that we are able to maintain AMR at the current level.

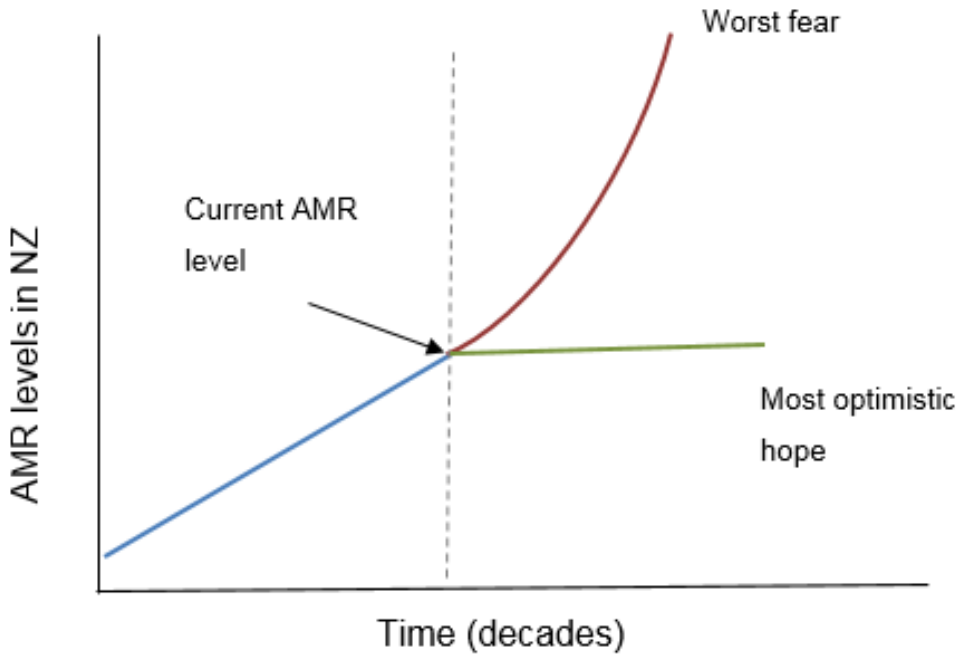

Figure 7.1 Stakeholder impressions of changes in AMR over time

People were generally more uncertain about trends of AMR in animals, noting limited data. Several interviewees commented that resistance levels in livestock in New Zealand is not currently a concern. A few noted that it seems from the data that is available, resistance levels in animals have not increased for some time.

7.2 Causal loop diagrams

The remainder of this chapter outlines the CLDs for the 13 sub-themes where feedback loops were identified. See section 5.2.1 for a reminder of causal loop diagram conventions. Reinforcing loops 'R' amplify processes, whilst balancing loops 'B' counteract and oppose change. In cases where the literature review articles included feedback loops that were not supported by interview content, these loops are represented using green arrows rather than the standard blue. Ideas from the research team about connections and loops that were not reflected in the interviews or literature review models are indicated in red. Larger versions of the CLDs in this chapter are available in the separate booklet (Appendix G). Variables linking feedback loops are retained in the simplified CLDs. Exogenous variables (factors identified as being important parts of the system, but not involved in feedback loops) are displayed in smaller font and with grey arrows in the enlarged CLDs provided in Appendix F. Balancing and reinforcing loops are numbered sequentially throughout the CLDs. Dotted lines indicate that the nature of the relationship between two variables was contested.

7.2.1 Pharmaceutical economics and antibiotic development

Two reinforcing loops and five balancing loops were constructed for this subtheme (Figure 7.2). Balancing loop 1 (B1 'basic use of antibiotics for treatment') is based on a feedback loop from Homer *et al.* (2000). This balancing loop communicates the idea that if there are greater numbers of sick and hospitalised people, the resulting physician visits are likely to result in antibiotic prescriptions. This antibiotic use feeds back to reduce the numbers of sick and hospitalised people. Although the interviews did not specifically raise this idea, links between antibiotic use and individual health were made by interviewees.

B2 ('AMR limits antibiotic use') illustrates interviewee's ideas that the more antibiotics are used, the more resistance becomes a problem. This undermines antibiotic effectiveness in the long term and therefore limits the amount of antibiotic sales, which may slow resistance. Many interviewees felt the limitation resistance imposes on antibiotic sales is a strong disincentive for pharmaceutical companies, who need to make up for the expensive investment in research and development (R&D).

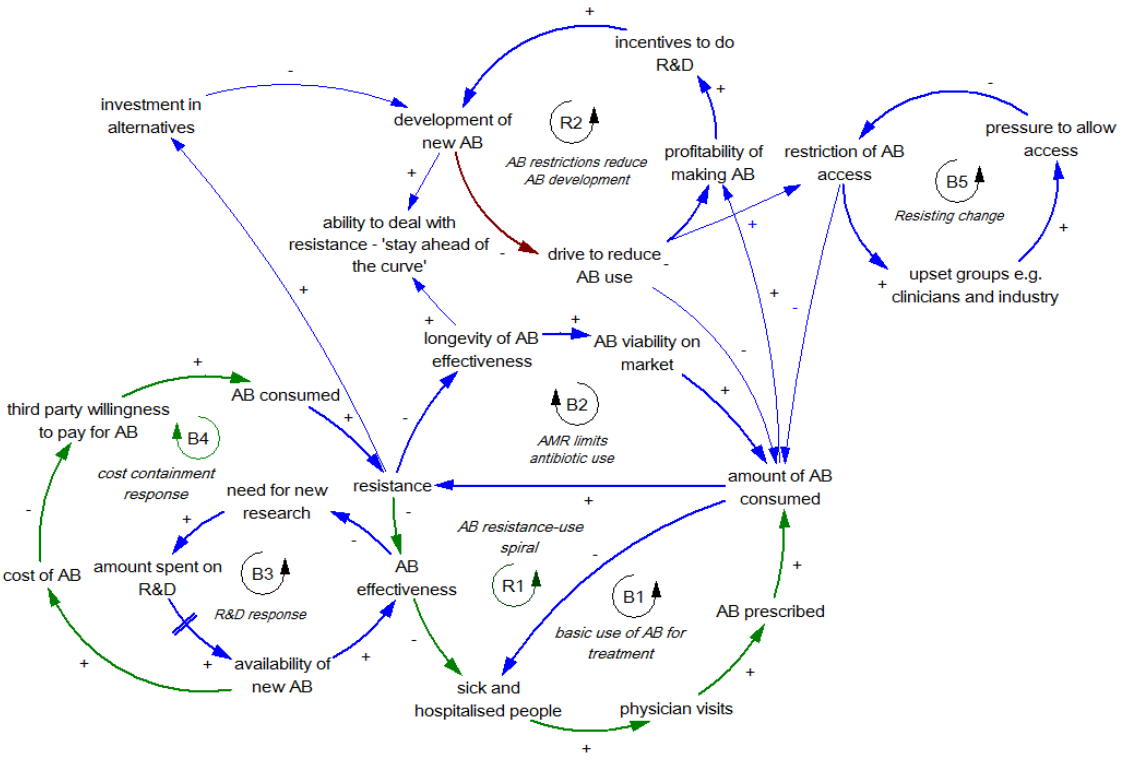

Figure 7.2 CLD: Factors affecting development of new antibiotics. See Appendix F for full diagram with exogenous variables.

Homer *et al.* (2000) suggested an alternative (reinforcing) feedback loop to describe the relationship between antibiotic use and resistance. This loop (R1 'antibiotic resistance-use spiral') is shown in green, and posits that use of antibiotics leads to resistance, which undermines the effectiveness of antibiotic treatment. This may increase the number of sick and hospitalised people, resulting in more physician visits and more antibiotics being prescribed, which further perpetuates resistance. This concept was not supported by the interviews.

B3 ('R&D response') is based on a feedback loop in the model from Homer *et al.* (2000), which was supported by the interviews. Participants described how as antibiotics become less effective, this results in the need for more research into antibiotic development, increasing the funding given to this venture. With a delay (my addition from the interviews to Homer's loop), this investment will increase the availability of new

antibiotics, improving the effectiveness of antibiotic treatment. The delay mark is justified by many participants' discussions of R&D as a lengthy process.

B4 ('cost containment response') is also based on a loop identified by Homer *et al.* (2000), which was not supported by the interviews. It posits that as resistance increases and more research and funding is put into developing new antibiotics, the cost of antibiotics may increase. This would likely reduce the willingness of third parties to pay for antibiotics, resulting in a reduction in the amount of antibiotics consumed and therefore reducing the problem of antibiotic resistance. Note that as the polarities of these links were not specified in Homer *et al.* (2000), I had to make assumptions about the likely polarity.

B5 ('resisting change') is based on the idea that restricting access to antibiotics would help preserve antibiotic efficacy; a disinvestment that could result in future health gain. However, it was thought that moves to restrict access to certain antibiotics would upset clinicians and industry groups, who would then increase pressure on regulatory agencies to allow access, countering the initial policy.

R2 ('antibiotic restrictions reduce antibiotic development') is a feedback loop that may counter B3. Antibiotic resistance naturally leads to policies aiming to reduce use, which diminishes the profitability of developing new antibiotics. Reduced profit potential was thought to be a key factor limiting R&D, resulting in low development of new antibiotics. This may further drive policies to limit antibiotic use as part of a reinforcing feedback loop. Conversely, if new antibiotics are developed this could possibly result in a relaxing of antibiotic stewardship (which would lead to more resistance, but would also increase the attractiveness of developing antibiotics). Many saw this coupling between antibiotic sales and pharmaceutical profits as problematic.

7.2.2 The politics of collaboration

Four reinforcing loops and one balancing loop were identified within the theme of collaboration (Figure 7.3). R3 ('competitive thinking') illustrates that some interviewees felt that a patch protection attitude is a problem in New Zealand, which results in people

wanting to take the credit for good ideas alone. This undermines sharing of ideas and strategies for combatting AMR, creating a vicious cycle that undermines collaboration.

The set of reinforcing loops on the right side of Figure 7.3 (R4 - R6: 'trust and blame', 'learning from each other', and 'effective action motivates working together') illustrate how good communication and sharing of ideas increases effective action and understanding between sectors. This reduces blaming of other groups and can become a virtuous cycle that promotes further collaboration (R4).

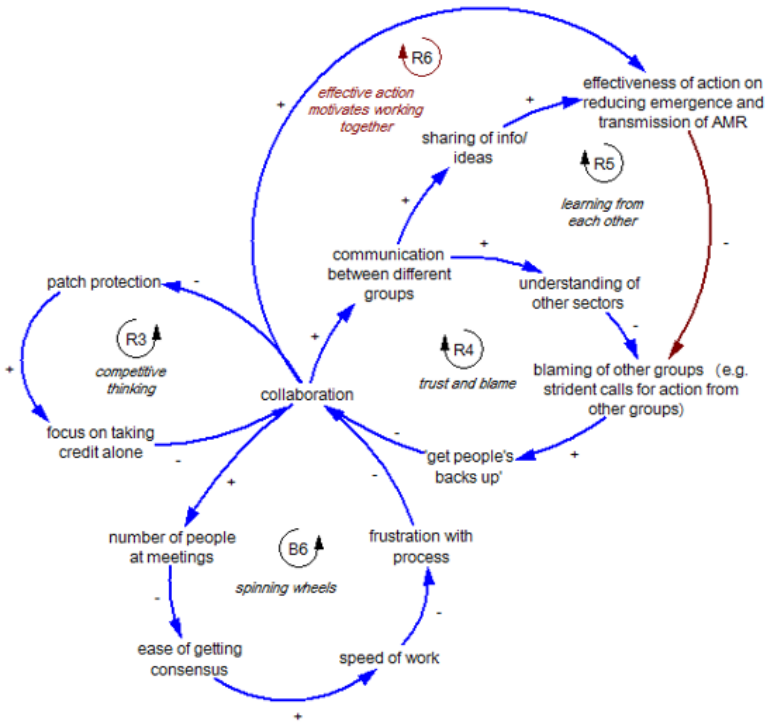

Figure 7.3 CLD: Politics of collaboration. See Appendix F for full diagram with exogenous variables.

R6 was identified by the research team as a possible feedback loop by which more effective action leads increased willingness to collaborate, which leads to more effective action.

A balancing loop (B6 'spinning wheels') was also identified in this collaboration sub-theme. It was pointed out that more collaboration generally calls for more people to be at meetings, which can make gaining consensus difficult. In the case of the AMR action group, the fact that many people are involved inconsistently was thought to slow

consensus building and therefore the speed of work. This can make people frustrated with the process and less inclined to want to collaborate.

7.2.3 Political prioritisation and funding

In Figure 7.4 below, R7 is slightly amended from the 'surveillance/funding spiral' in Homer *et al.* (2000). The interviews supported the idea that the more funding of AMR research and action there is, the more surveillance infrastructure there is likely to be. This will increase the amount of surveillance hits, garnering more media attention. Hopefully this would increase political prioritisation of the issue and lead to more spending on AMR in a reinforcing loop. However, some interviewees noted that unfortunately, surveillance doesn't always lead to action.

The connected reinforcing loop (R8 'public pressure affects political priorities') displays interviewees ideas that increased media attention on the topic of AMR will increase public understanding of the issue, leading to increased pressure on the government to act. However, this media coverage needed to be accurate and informative, not 'scaremongering'.

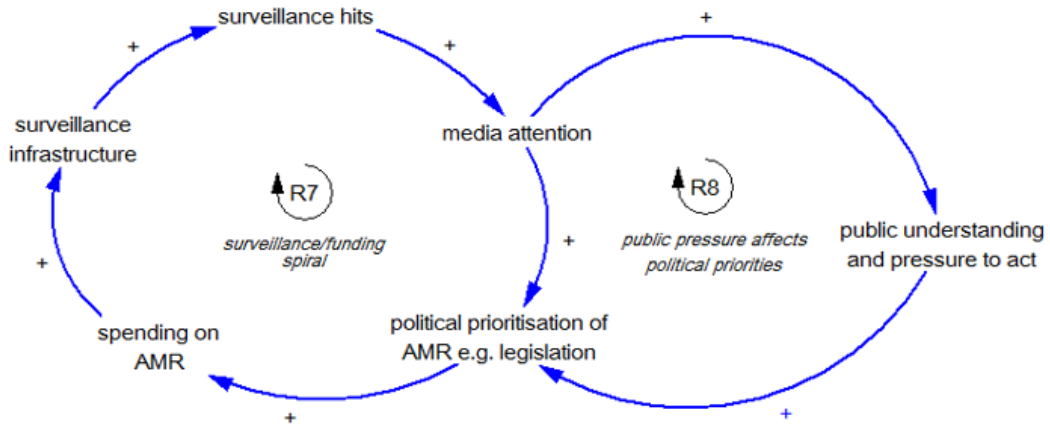

Figure 7.4 CLD: Political prioritisation of AMR. See Appendix F for full diagram with exogenous variables.

7.2.4 International influences

Figure 7.5 shows a feedback loop that was identified within the theme of international influences. Interviewees discussed how high levels of AMR overseas were said to increase travellers' likelihood of exposure, and the risk of returning home carrying resistant microbes. Given the global nature of AMR, as AMR levels rise there may be increased attempts at global governance and international restriction of antibiotic use (R9: 'international context'). This would further limit pharmaceutical profitability of making antibiotics, which could have the unfortunate effect of further driving production to countries were labour is cheap and environmental regulations are low. This would act to reinforce the cycle by further raising levels of AMR in these countries.

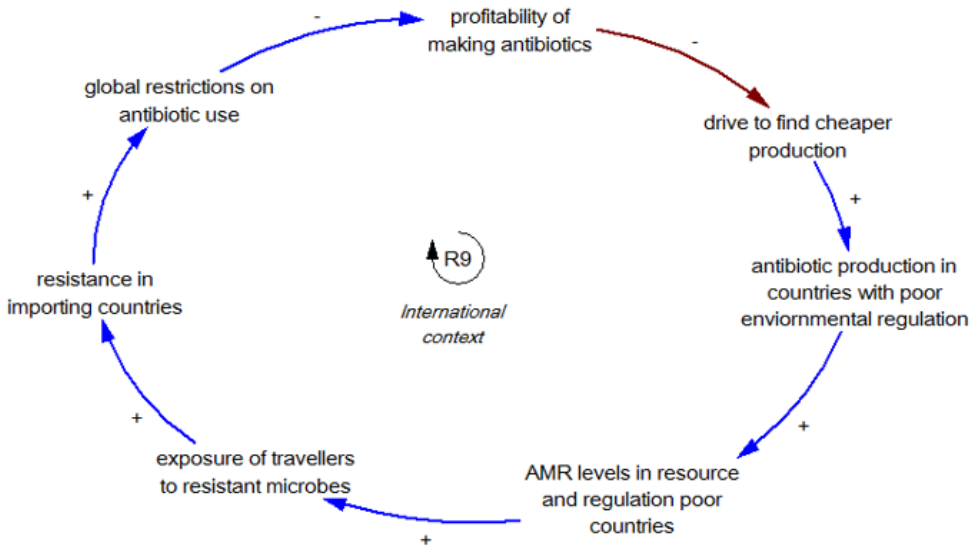

Figure 7.5 CLD: International influences on AMR. See Appendix F for full diagram with exogenous variables.

7.2.5 Drivers and impacts of antibiotic use in food producing animals

The CLD describing influences on animal antibiotic use (Figure 7.6) consists of two reinforcing loops and five balancing loops. Both balancing and reinforcing loops link to the perception that antibiotic use in FPAs improves productivity. Links between antibiotic use and resistance in animals are shown using dotted lines because although

most interviewees agreed that more use leads to higher levels of AMR, some thought we haven't seen clear evidence to support this.

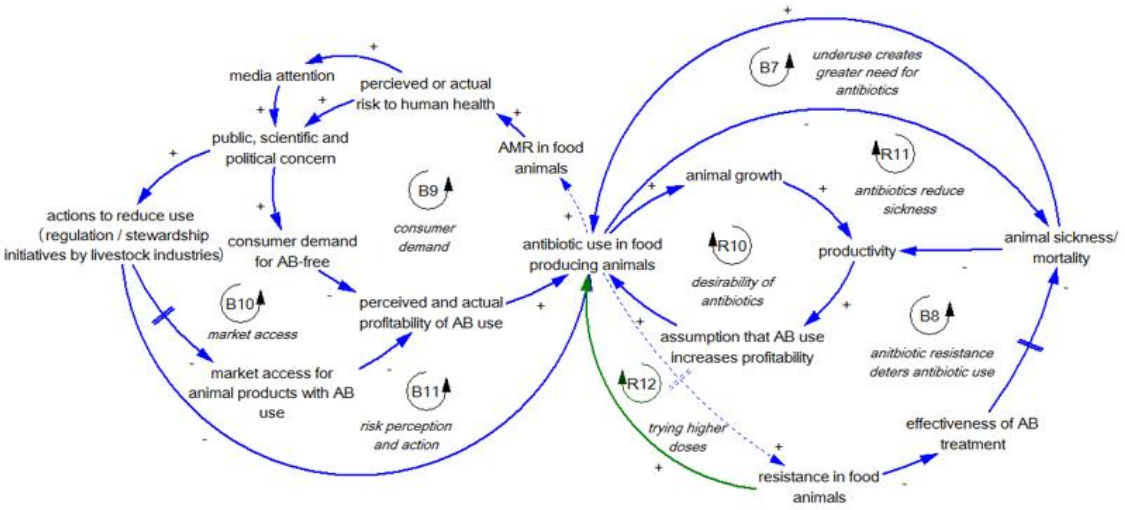

Figure 7.6 CLD: Influences on antibiotic use in food animals. See Appendix F for full diagram with exogenous variables.

R10 'desirability of antibiotics' may be acting to encourage increased antibiotic use in food animals. Several interviewees talked about how antibiotic use in food animals can improve productivity (and therefore farmer profit margins), for example by encouraging faster weight gain (R10). This was thought to increase the assumption that antibiotics improve economic efficiency. This leads to more antibiotic use, which increases productivity, and so on, in a reinforcing feedback loop. A connected reinforcing loop (R11 'antibiotics reduce sickness') is that antibiotic use helps reduce animal sickness and mortality, improving productivity and further driving R10.

R12 ('trying higher doses') is based on a feedback identified by Henriksson *et al.* (2018). They postulated that in the aquaculture sector, increasing levels of AMR results in use of more antibiotics, in an attempt to over-come reduced microbe sensitivity (e.g. trying higher doses). This was not a concept discussed by the interviewees.

Some interviewees talked about how if less antibiotics are used, animals will be at higher risk of infection, which would result in more antibiotic use (B7 'underuse creates greater need for antibiotics'). An example discussed was that if less antibiotics are used for growth promotion and prophylaxis, more animals may become sick and require

therapeutic levels of antibiotics, which could result in greater use overall. One person did note that this increase in therapeutic antibiotic use following restrictions in sub therapeutic use can be a temporary effect.

Another balancing loop (B8) could be described as 'antibiotic resistance deters antibiotic use'. Use of antibiotics drives higher levels of antibiotic resistance in food producing animals, which will reduce effectiveness of antibiotic treatment, meaning food animals have higher levels of morbidity and mortality. This will reduce farm productivity and weaken the assumption that antibiotics improve economic efficiency, likely resulting in less antibiotic use. However, it may take some time for resistance levels for a particular antibiotic to reduce after removal of that antibiotic (delay mark). Some interviewees thought that once resistance levels are higher than a certain unknown 'tipping point', restriction of a particular antibiotic may have little effect. Another delay area could be in discovering that reduced antibiotic effectiveness is due to resistance (as opposed to, for example, simply using the wrong antibiotic for an infection). These delays may make B8 relatively weak and slow to have an effect.

A set of balancing loops (B9, B10, B11) relate to the perception of risk to human health, resulting in less use of antibiotics in FPAs. B9 'consumer demand' shows how international regulations and market demand for low antibiotic use will affect the way farmers perceive the profitability of using antibiotic and further drive down antibiotic sales and use. Also, if farmers use antibiotics their products will be seen as less desirable, reducing their profit and therefore meaning they have less money available to buy antibiotics anyway.

B10 'market access' shows how perception of risk by health authorities and consumer demand for antibiotic free animal products can also drive such actions (e.g. the EU banned the use of antibiotics as growth promoters in 2006, and moves to restrict metaphylaxis and prophylactic use are currently underway). Countries are also beginning to put standards in place for antibiotic use in animal products they import.

B11 'risk perception and action' is similar to the 'media and public pressure' feedback loop by Grohn *et al.* (2017). As more antibiotics are used in FPAs and more concerns are

raised about possible transmission of resistance from animals to humans, there is a growing perception of risk to human health (amongst researchers, policy makers/regulators, and the public). Increased media attention will also facilitate public awareness and concern. Public concern about the issue is likely to increase pressure on those in power to act, resulting in moves to reduce antibiotic use in FPAs (e.g. stronger regulation, better stewardship).

7.2.6 Industry influence, public pressure and political will

The CLD below (Figure 7.7) connects to the CLD in Figure 7.6, as the loops involved will drive the amount of antibiotics used in animals. Two reinforcing loops and one balancing loop were synthesised from the theme of how industry influence and public pressure may affect political will to act on antibiotic use in animal agriculture.

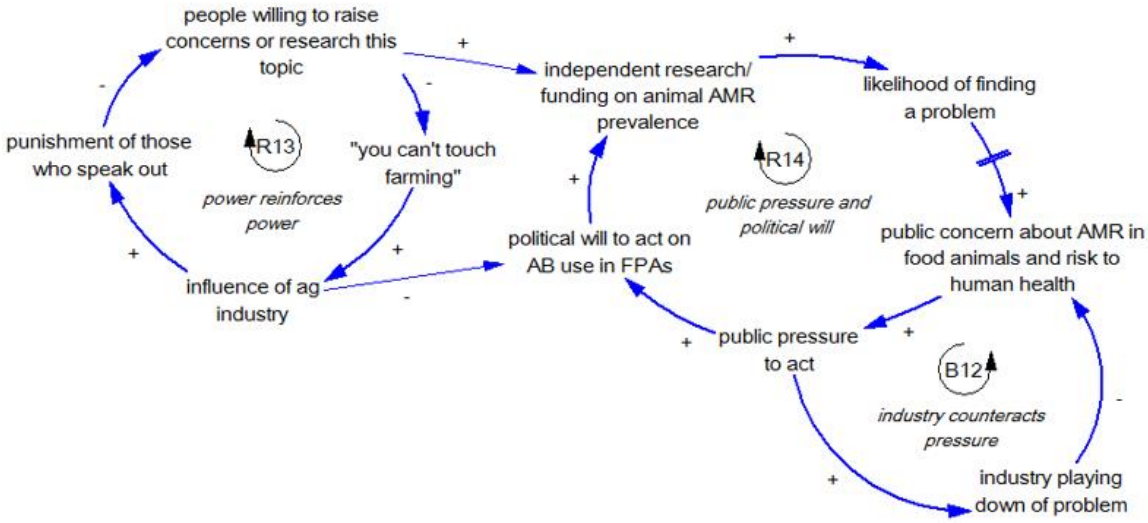

Figure 7.7 CLD: Industry and public influences on AMR action. See Appendix F for full diagram with exogenous variables.

R13 shows a reinforcing loop where 'power reinforces power'. One interviewee noted that power of the agricultural industry can result in punishment of people who speak out, which may result in less people being willing to raise concerns or delve into the topic. This further reinforces the perception that farming practices are unquestionable, as well as reducing independent research.

R14 ‘public pressure and political will’ reflects the perception among participants that more political will to act would increase the amount of independent research and funding related to determining AMR prevalence in animals. Levels of public concern are likely to rise or fall directly in response to reported resistance levels and in turn influence political action. However, a balancing loop (B12: ‘industry counteracts pressure’) reflects a view that public pressure may cause industry to downplay the seriousness of the problem, reducing public concern and weakening the pressure to act.

7.2.7 Structural inequities increase vulnerability to infection

Five reinforcing loops were synthesised relating to structural inequities that drive vulnerability to infection (Figure 7.8).

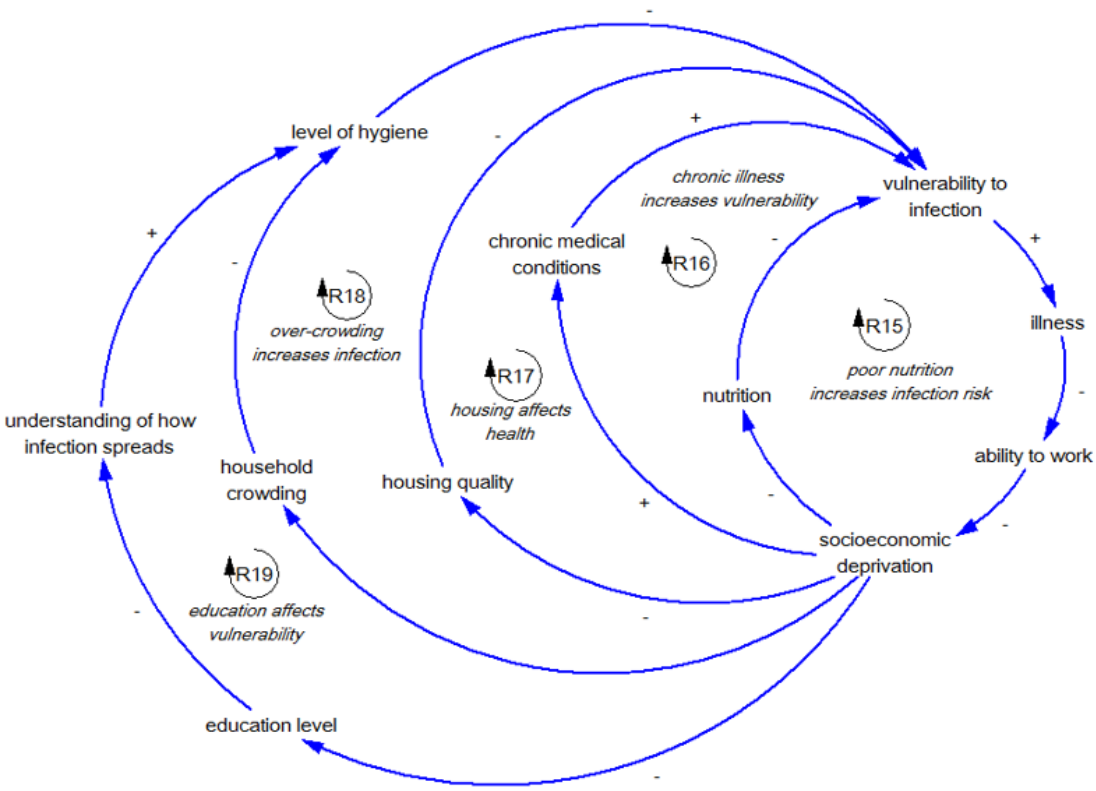

Figure 7.8 CLD: Structural inequities drive vulnerability to infection. See Appendix F for combined CLDs for Figures 7.8, 7.9 and 7.11, with exogenous variables.

Many interviewees expressed concern about how socioeconomic deprivation could play an important role in vulnerability to infection, via multiple pathways: via poor nutrition (R15), chronic illness (R16), low housing quality (R17) and household crowding (R18).

Deprivation was also thought to limit educational opportunities, possibly resulting in less understanding of how infection spreads (R19). Lack of knowledge combined with other barriers resulting from living circumstances were thought to have an effect on hygiene and infection prevention practices, putting people at increased risk of infection. This affects both the amount of bacteria in the community environment and how easily they are transmitted between people. All these loops (R15 - R19) can increase susceptibility to infection. Overall this means people are more likely to be unwell and unable to work (as well as being likely to receive antibiotics, which could drive resistance). This further limits income and increases deprivation, reinforcing the above vicious cycles.

7.2.8 Factors driving AMR transmission in the community

Several participants talked about the idea that 'prevalence drives incidence' (R20 in Figure 7.9). A higher prevalence of infectious disease means that more people will be at risk of exposure, and therefore vulnerable to infection, driving incidence of disease. Higher incidence reinforces higher prevalence. This is similar to the 'contagion spiral' from Homer *et al.* (2000).

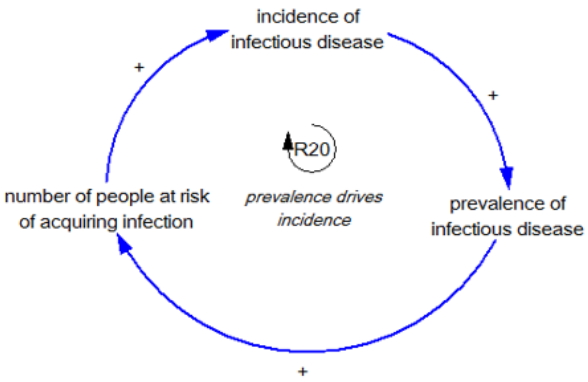

Figure 7.9 CLD: Prevalence drives incidence in the community

7.2.9 Drivers of antibiotic prescription and factors affecting stewardship

R21 ('setting a precedent') in Figure 7.10 illustrates the perception by some interviewees that historical over-prescription of antibiotics has created a situation where it is difficult to back-track. Over-prescription in the past, including as placebos, has normalised antibiotics for both patients and clinicians. This leads to patients having high expectations of receiving antibiotics for even minor ailments, increasing pressure on clinicians to prescribe and reinforcing over-prescription.

Antibiotics were also described as powerful anxiolytics (R22) – both the prescriber and the patient tends to feel better when they are prescribed. Normalising of antibiotic use may feed patient anxiety about infection, putting further pressure on clinicians to prescribe antibiotics.

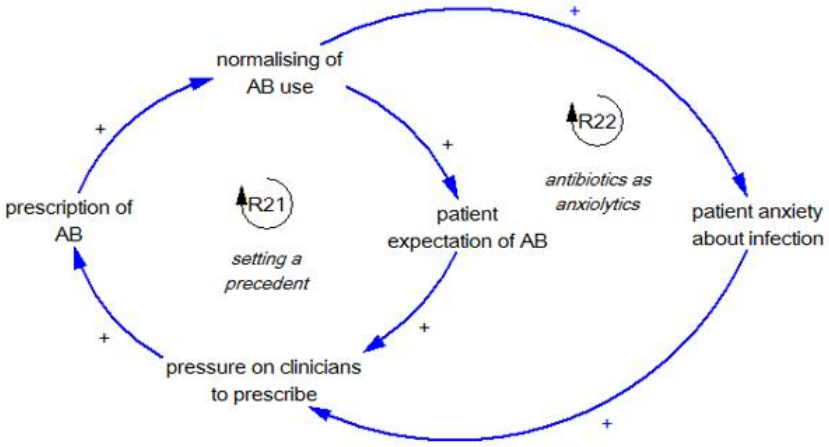

Figure 7.10 CLD: Drivers of antibiotic prescription

7.2.10 Emergence and transmission in health and care settings

Two reinforcing loops (R23 and R24 in Figure 7.11) were identified that can make patients more vulnerable to infection in a hospital setting. Interviewees referred to the risk of increased numbers of potentially pathogenic microbes in hospital. Longer stays in hospital increase the length of time patients are exposed to potential infection, making them likely to become more ill and have to stay longer (R24). Several interviewees posited that the longer someone stays in hospital, the more likely it is that the integrity of their skin barrier will be compromised due to more IVs, catheters, bed sores etc. The skin is a key barrier to infection, and the importance of managing skin health to reduce

the risk of acquiring and transmitting bugs was commonly mentioned. Compromised skin integrity increases likelihood of infection, which may further prolong a stay in hospital (R23).

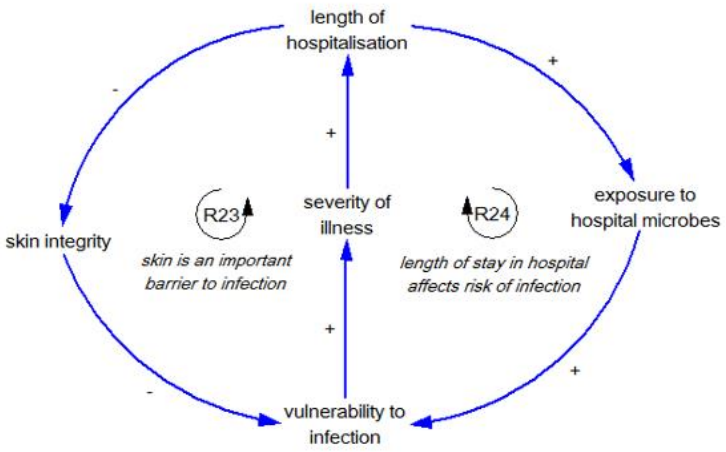

Figure 7.11 CLD: Factors increasing vulnerability to infection in the hospital context

7.2.11 Unintended consequences of antibiotic use in humans

Two interconnected balancing loops were constructed from participants' ideas about the unintended effects of antibiotic use (Figure 7.12).

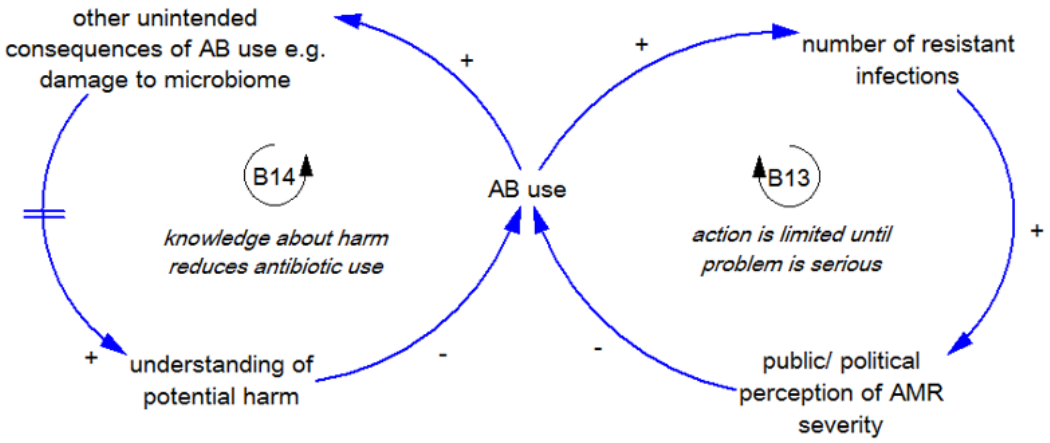

Figure 7.12 CLD: Unintended effects of antibiotic use leads to action

Some participants considered that in New Zealand we may be relatively protected from antibiotic resistance initially, due to vaccination coverage, generally good sanitation and good nutrition as compared to developing countries. It was thought that this could create some inertia on the issue of AMR, limiting public and political concern about the

problem. However, as B13 ('action is limited until problem is serious') in the above CLD shows, as resistant infections rise and AMR starts to have more obvious and direct impacts on more people, this will likely increase public and political concern about the problem, resulting in policies and personal actions to reduce inappropriate use of antibiotics. This may stall the progress of resistance.

A small number of interviewees also talked about other possible unintended consequences of antibiotic use. This was said to be an area of increasing research and concern. Antibiotic use can disrupt the normal microbiome, and this damage to our natural flora may be a pathway in the aetiology of conditions such as Type 2 diabetes, obesity, heart disease and autoimmune problems (B14). There is also the more well-known contribution to *Clostridium difficile* (this bacteria can cause gastro-intestinal issues following use of antibiotics). B14 ('knowledge about harm reduces antibiotic use') suggests that as these kinds of problems become more prevalent and better researched (which may take some time, as indicated by the delay mark in the diagram), physicians and patients may start to shift away from the perception that antibiotics only do good, resulting in less unnecessary use.

7.2.12 Water quality and AMR

As displayed in Figure 7.13, two balancing loops were synthesised for this theme. B15 ('complacency about fresh water') represents interviewees' discussion around how New Zealand has historically been considered as 'pure, clean and green' with pristine water. One interviewee said that for a long time we haven't had to worry about water quality, possibly leading to public and political complacency about preserving water quality. Lack of pro-activeness has led to the current culminating issues around fresh water, and several interviewees were particularly concerned about impacts of agricultural intensification on water quality. As the problem worsens and awareness and concern rises, action is more likely. However, there could be a time delay before we see physical improvements in water quality resulting from action. Contamination here includes antibiotics, bacteria, and herbicides, pesticides, and other chemicals. B16 ('poor water quality drives water treatment') illustrates that as water quality worsens and public and

political concern increases, action may include better water treatment to help balance water quality.

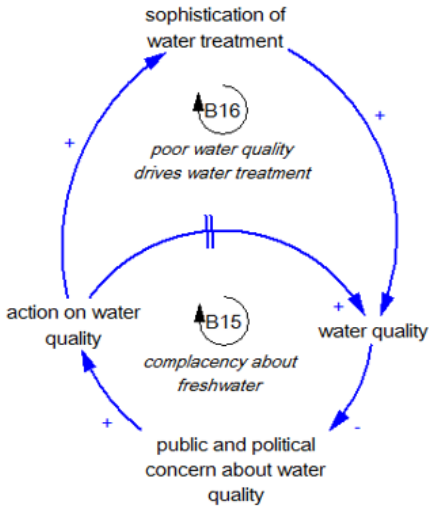

Figure 7.13 CLD: Water quality and AMR. See Appendix F for full diagram with exogenous variables.

7.2.13 Chemical co-selection of antibiotic resistance

A reinforcing loop was constructed under this theme of co-selection (Figure 7.14).

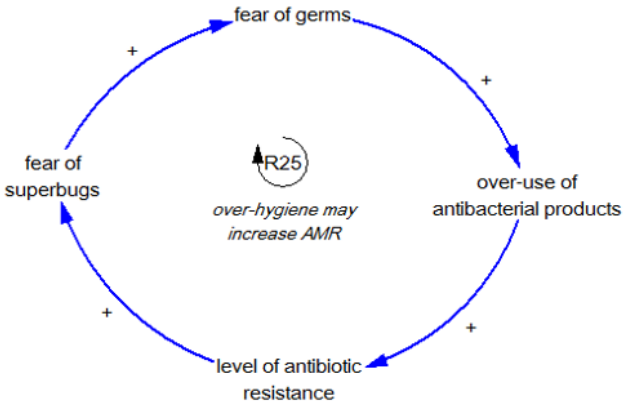

Figure 7.14 CLD: Superbugs. See Appendix F for full diagram with exogenous variables.

Fear of germs may lead to over-use of antibacterial agents, which paradoxically may increase levels of resistance. As AMR increases, fears of 'superbugs' and germs in general may increase, resulting in even more use of antibacterial agents (R25).

7.2.14 Overall model

Figure 7.15 below shows the integration of the previously discussed feedback loops, omitting exogenous variables for clarity. Please see the attached A3 page (with the separate booklet, Appendix G) for a larger version. 'Level of AMR in humans' was a central variable with many interconnections, so this is emphasised in the overall model.

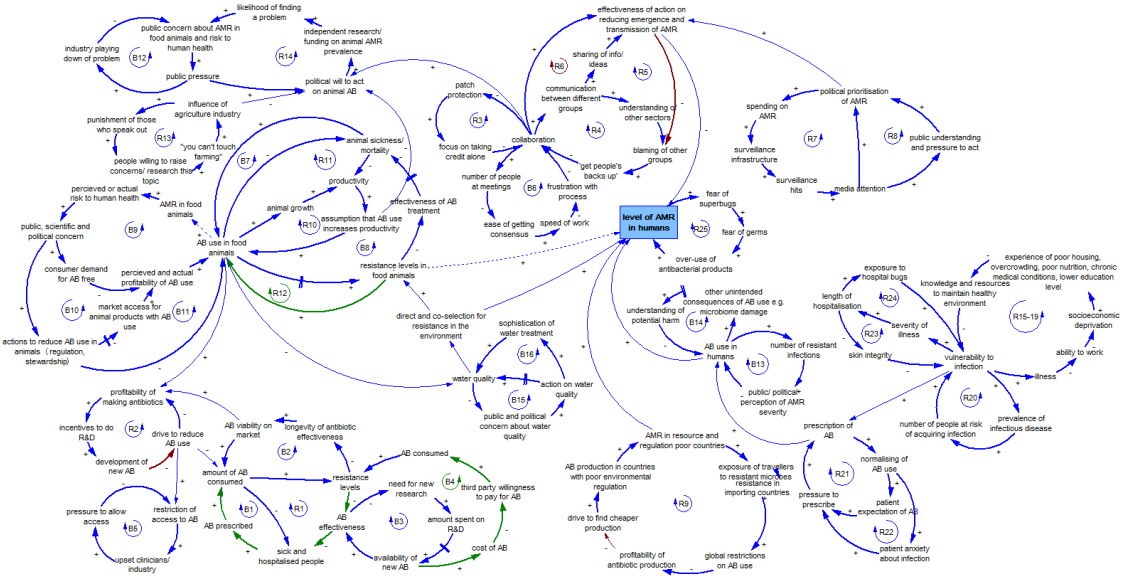

Figure 7.15 Overall model

7.3 Summary

This chapter began by describing the varied perceptions participants had about how AMR has changed over time, and their hopes and fears for the future. It then described causal loop diagrams that were associated with sub-themes. Next, for the final chapter of this thesis, I discuss what the results of this participatory system dynamics approach mean in a wider context and their possible implications and suggest directions for future research.

8 Discussion

This thesis has aimed to answer the questions:

1. *What are the relationships between different aspects of human, animal, and environmental health in relation to antimicrobial resistance, within the New Zealand cultural and political context, as perceived by a variety of stakeholders?*
2. *What are the feedback loops that are driving trends in AMR over time in New Zealand?*

In this chapter I summarise the main findings of my research and discuss their meaning, contextualise the results within the wider literature to highlight what this study adds, discuss strengths and limitations of my study, consider implications of the study, and make recommendations for future research.

8.1 Summary and interpretation of the principal findings

8.1.1 Stakeholder perspectives on One Health aspects of AMR

My findings show that experts in New Zealand have diverse (and sometimes contradictory) perspectives on the causes and effects of antibiotic resistance in New Zealand. Whilst all agreed that levels of resistance in humans and animals has been increasing over time, participants disagreed about the exact pattern of AMR growth. This may indicate there is a real need for better surveillance data to more comprehensively establish how resistance levels for different organisms are changing, which could help different stakeholders come to a shared view of the severity of the problem.

Collectively, interviewees saw AMR as a highly complex issue, with many human, animal and environmental factors involved and inter-linked. However, there was no overall consensus between interviewees as to which factors are the most important drivers of AMR in New Zealand. The range of causes and effects of AMR discussed by interviewees corresponded well with my background reading, representing a wide range of knowledge and opinions. Disagreement about the relative importance of each sector may stall action in reducing antibiotic use, which will be required to reduce AMR. The themes resulting from the thematic analysis are summarised next.

AMR is set within a **broader political and economic context**, with strong international influences. There are many complex barriers to the development of new antibiotics which can be linked to the profit-dependent nature of pharmaceutical companies. However, simply creating new antibiotics is unlikely to solve the AMR problem. Collaboration between different disciplines appears to be improving in New Zealand, but blaming and limited trust between some groups is still an issue. AMR is not high on the political agenda, which limits our ability to address it. Resistance is an international issue, and many of the resistant infections in New Zealand are likely to have originated overseas.

The impact of **antibiotic use in food producing animals** on human health was an area of disagreement in the interviews, a debate which is also reflected in the literature (8, 61, 65). Some interviewees saw antibiotic use in food animals as a threat to human health, while others were more sceptical of such links. There was also some disagreement around whether greater intensity of agriculture drives more use of antibiotics. Some interviewees expressed concern about the strength of the agricultural lobby in New Zealand, while others stressed the precautionary approach livestock industries take to antibiotic use. The issue of antibiotic use in food producing animals was clearly linked with wider political and economic contexts, through discussion of underlying economic motives for antibiotic use, political influence of industry, and discussion of the intensification of agriculture.

Factors that increase the **risk of infection and transmission of AMR in the community** was another overarching theme. Vulnerability of different groups to AMR was frequently linked to wider structural inequities in New Zealand, including issues of poverty and income inequity, housing quality, and inequities in access to healthcare by income and ethnicity. This theme was therefore also linked more broadly to the political and economic context of New Zealand. Individual level characteristics were also considered. The closeness of interactions between humans and companion animals may also increase risk of AMR transmission.

Levels of **antibiotic stewardship and transmission of AMR in health and care settings** was another important theme. General Practitioners face many pressures to prescribe antibiotics, and community prescribing was widely seen as the main contributor to the problem of AMR in humans. Hospital prescribing was generally thought to be

more regulated. On the other hand, the risk of AMR and transmission of resistance was thought to be higher in health-care compared to community settings. As well as AMR, other possible unintended consequences of antibiotic use were also contemplated.

Several interviewees saw **the environment** as an important but poorly understood aspect of AMR. Concern was raised about antibiotics and resistant bacteria entering the environment from farm runoff and urban wastewater. The environment theme was therefore closely linked to the issue of antibiotic use in food animals. Higher background levels of AMR in the environment was thought to increase the risk of transfer of resistant genes to pathogens of human significance. Water quality was seen as a very relevant aspect of the AMR picture. Co-selection of AMR as a result of use of chemicals such as commercial cleaners, herbicides and pesticides is another potentially significant contributor to AMR.

This research has highlighted some of the complexities, disagreements and contradictions surrounding the issue of AMR, confirming that AMR is a classic complex problem with multiple stakeholders and policy resistance. Participatory system dynamics modelling is likely to be a particularly helpful approach in such situations.

The political and economic environment was a cross-cutting idea across many of the above themes. This demonstrates that antimicrobial resistance is inextricably linked to high-level drivers beyond the control of most individuals. A small number of interviewees specifically linked AMR to capitalism, particularly in relation to the profit-driven model of antibiotic development and the macroeconomic incentives for antibiotic use in agriculture. Many of the structural inequities in income, housing and healthcare access discussed by interviewees are also a result of similar macroeconomic policies. Therefore, it is likely that addressing antimicrobial resistance will require a shift in our political approach to economic policy, to prioritise reducing inequities and create a system for antibiotic development that is based on the social good of antibiotics. Many of the current strategies for addressing AMR tend to focus on technological and biomedical solutions, but greater acknowledgement of AMR as a fundamentally socio-economic and political problem is needed (18).

8.1.2 Feedback loops driving trends in AMR in New Zealand

Causal loop diagrams were developed based on the thematic analysis, cognitive maps, literature review, and supervisory expertise. CLDs were developed for 13 of the 19 interlinked subthemes identified in the thematic analysis, summarised below.

1. Five balancing loops and two reinforcing loops were synthesised for the subtheme **'pharmaceutical economics and antibiotic development'**. Most of the balancing loops represent barriers to development of new antibiotics, which could indicate progress in this area is unlikely under current profit-driven models of drug development.

2. Under the theme of **'politics of collaboration'**, four reinforcing loops and one balancing loop emerged. Improved collaboration would result in these reinforcing loops operating as 'virtuous cycles', fostering improved communication and reducing blame between sectors. However, the balancing loop also needs to be managed in the process of encouraging collaboration, to ensure that the large numbers of people at meetings don't result in reduced communication and increased frustration.

3. The **'political prioritisation and funding'** subtheme illustrated how increased political prioritisation of AMR, such as spending on surveillance, may give a clearer picture of the problem, garnering media attention and pushing further political action. This was also thought to be mediated through public understanding of the issue and pressure on politicians.

4. The single loop synthesised for the **'international influences'** subtheme illustrated the fact that AMR is a global issue. It shows that policies to restrict antibiotic use may paradoxically push more antibiotic production into resource and regulation-poor countries, further contributing to the global level of AMR.

5. The '**drivers and impacts of antibiotic use in food animals'** subtheme comprised three reinforcing loops and five balancing loops. As established in the background chapter, global use of antibiotics in food animals is increasing. Hence

it is reasonable to postulate that the reinforcing loops may currently be dominating: despite the side effects of antibiotics and increasing restriction of their use, their perceived positive impact on productivity may currently be stronger. However, as resistance levels increase and concern about transmission to humans reaches a tipping point, the reinforcing loops may become less dominant; antibiotic use may not seem so desirable or profitable, which could result in less use and help contain AMR.

6. The CLD for the **'industry influence, public pressure and political will'** subtheme comprised two reinforcing loops and one balancing loop. The loop showing that 'power reinforces power' could bolster the influence of the agricultural industry, which some interviewees thought would result in less political will to restrict antibiotic use in animals. It was thought that independent research on AMR in animals would be more likely to find a problem than commercially funded research, resulting in public pressure on politicians to act. However, there was also the idea that industry would react to downplay the seriousness of the problem and placate public fears.

7. The CLD for the **'structural inequities increase vulnerability to infection'** subtheme consists of five reinforcing loops and no balancing loops. Poor nutrition, chronic illness, poor housing quality, overcrowding and reduced education as a result of deprivation were all thought to play a role in increasing the vulnerability of some groups to AMR. Vicious cycles of deprivation may be key area to target in the fight against AMR.

8. The one reinforcing loop for the **'factors driving AMR transmission in the community'** subtheme illustrates the epidemiological observation that prevalence drives incidence.

9. The two reinforcing loops under **'drivers of antibiotic prescription and factors affecting stewardship'** show how normalising prescription of antibiotics may have set a precedent, resulting in high patient expectations of antibiotics that are difficult to shift. This is further driven by use of antibiotics to relieve anxiety about infection for both patients and prescribers.

10. Two reinforcing loops under the **'emergence and transmission of AMR in health and care settings'** subtheme display how longer hospital stays may increase risk of acquiring resistant infections.

11. On the other hand, the two balancing loops under **'unintended consequences of antibiotics use in humans'** illustrate how rising numbers of resistant infections, as well as learning about other harmful effects of antibiotics, may help to reduce antibiotic use.

12. The **'water quality and AMR'** CLD consisted of two balancing loops, that illustrated how as water contamination reaches a critical threshold, public and political complacency about water quality may be over-come. Action on water quality may help reduce the co-selection of antimicrobial resistance in the environment.

13. In a related subtheme **'chemical co-selection of antibiotic resistance'**, the reinforcing loop illustrates that a fear of germs and overuse of antibacterial products may paradoxically worsen our problem with antimicrobial resistance.

While these 13 CLDs were presented separately for clarity and simplicity, they are inextricably intertwined. Therefore, I have also brought them together into an overall model of the AMR system in New Zealand to demonstrate this, and show where the connection points are (Figure 7.15). A total of 41 loops were synthesised for the overall model. Of these, 25 were reinforcing loops and 16 were balancing loops. Eight of the loops were based on feedbacks identified in the literature review (39, 80, 88-90, 113). Four of these loops also appeared in the interviews, and four did not. The remaining 33 feedback loops were entirely new.

8.2 What this study contributes

This is the first time internationally that participatory system dynamics modelling has been used to create an integrated model of the human, animal and environmental aspects of AMR. Very few previous models have explicitly represented a proposed structure of

the AMR system in diagram form that incorporates two or more of human, animal, and environmental domains, and none have done so comprehensively. It also appears to be the first such study explicitly underpinned by One Health and EcoHealth principles. These frameworks have proved useful in guiding this research, and have aligned well with my values of equity, sustainability, and stakeholder inclusion in the research process.

Despite increasing calls for One Health approaches to the issue of AMR, there is a significant gap in implementing this in an integrative way. The studies that met the inclusion criteria for the literature review tended to focus on modelling the transmission of resistance from animals to humans, with varying levels of complexity. Some included a small reference to the environment as a transmission pathway or reservoir of AMR, but this dimension was generally under-investigated. Most included some reference to policy, but specific policy recommendations arising from the models were not often discussed.

The literature review showed that system dynamics modelling holds potential for integrated modelling of AMR, but as yet this potential has not been fully realised. There was a clearly identified need for a model that included all three domains, with an explicit focus on feedback loops. Previous modelling efforts which used system dynamics methods were often limited by a lack of focus on feedbacks, and in some cases did not use standard SD conventions. Participatory modelling had also been under-utilised in these modelling efforts, despite recent recognition that this may be a useful way to operationalise systems thinking and One Health (20, 30). This research has sought to address the above mentioned gaps in AMR modelling.

In total, the previous models included eight feedback loops related to AMR. The interviews supported four of these, and also identified 33 new feedbacks for further exploration. Loops from the literature review that were supported by the interviews included the R&D response of pharmaceutical companies (39) and the surveillance and funding spiral (39). The ‘risk perception and action’ loop was similar to the ‘media and public pressure loop from Grohn *et al.* (2017), and the ‘prevalence drives incidence’ loop is similar to the contagion spiral in Homer *et al.* (2000). The four loops not supported by

the findings of this thesis were: ‘resistance use spiral’ (39), ‘resistance leads to more antibiotic use’ (113), ‘basic use of AB for treatment’ (39) and ‘cost containment response’ (39). It is possible that further discussion with the participants in this research would support the incorporation of these feedbacks into the New Zealand model of AMR.

The large number of novel feedback loops found in this study clearly highlights the complexity of AMR. This also appears to be the first time that balancing complexity and outlining stakeholder understandings has been the explicit purpose of an AMR model.

In keeping with previous research (18, 85), my findings clearly show that AMR is far more than just a biological issue; there are wider social, political and economic forces involved. The many feedback loops and interconnections between factors illustrate that changes in one variable can have far reaching effects. This study has demonstrated that there is more to AMR than specific microbe level or population transmission models. Although microbe-level and population transmission models are important for learning about AMR, this project has shown that wider economic and political drivers, which have largely been absent from previous research, are important for effective AMR policy.

One Health and EcoHealth frameworks have been useful in guiding my research, and have aligned well with my values of equity, sustainability, and stakeholder inclusion in the research process. Participatory system dynamics has proved to be a useful method for operationalising the integrative and systems thinking principles demanded by One Health and EcoHealth. The underlying principles EcoHealth were very useful for guiding my research process.

8.3 Evaluation of the study

8.3.1 Strengths

This study had a number of strengths. It has been novel in terms of approach – as far as we know, it is the first participatory system dynamics study on AMR that explores all three of the human, animal and environmental dimensions of the problem. It also appears to be the first such study explicitly underpinned by One Health and EcoHealth principles.

The study involved a large number of interviews, allowing for a diverse range of perspectives on AMR to be included, successfully representing all parts of the sampling frame except for one (community environment). Interviews generate rich descriptions of processes, causal understandings and feedback (191). By the end of the interviews I reached information saturation in terms of suggested causes and effects of AMR in New Zealand. Face-to-face interviewing may improve rapport building and facilitate more detailed answers compared with telephone interviews (192, 195). Face-to-face interviews enabled me to undertake cognitive mapping during the interviews.

Building rapport between the researcher and participants is important, especially for building trust in a participatory modelling process. Participants expressed their appreciation of the efforts to involve them in the project, including travelling around the country to meet with them face to face. I believe that meeting them in person made it easier to develop a connection and for interviewees to talk more openly. Giving participants the option to check their transcripts and cognitive maps was designed to also build trust in the research (although some commented they did not enjoy reading their transcripts). Most of those who replied regarding the cognitive maps commented that they were happy with the content, or that while they did not necessarily understand the conventions of such diagrams, the points they raised seemed to be covered. Almost all interviewees expressed interest in being kept informed of possible future work involving a group workshop.

In this research I have addressed some of the issues of validity and quality I identified in previous modelling studies. I explicitly aimed to enhance the transparency and usefulness of the process and model by: having a clearly articulated purpose; using an a-priori participant sampling strategy to identify participants; shaping interview questions to elicit a model that is fit for purpose; ensuring the interview transcripts and cognitive maps reflected the mental models of participants (by double checking of interview transcripts, participant approval of transcripts and cognitive maps); striving for balance between complexity and simplicity to ensure the model is both comprehensive and understandable; and ensuring correct use of SD modelling language and identification of feedbacks, so that my model can be easily recognised as a system dynamics model.

The focus on feedback loops in this preliminary SD model is a strength of this study. Although we have not yet tested the comprehensibility of the CLDs with participants, there is existing evidence that causal loop diagrams can allow quick and effective communication about the key components and interactions in a system (196). This provides some justification for a claim that the model will be useful for decision-makers, once refined and validated. This preliminary model has provided a transparent, comprehensive starting point for future work to build on.

In addition, I am unaware of any other study that has sought the views of such an extensive group of stakeholders on the matter of AMR in New Zealand, building on the work of Majowicz *et al.* to identify non-traditional stakeholders (90). This research has built the foundation for a participatory system dynamics process by carrying out the critical initial steps of stakeholder assessment and preliminary interviews (166). Interactive group participation will be the next stage of the process.

8.3.2 Limitations

The gaps in representation are one limitation of this research. Finding representation in the community aspect of the framework was the most difficult. A representative from a community organisation advocating on AMR from an environmental perspective could not be found within the timeframe of this thesis. This may indicate that AMR is not yet on the agenda of the environmental NGO community in New Zealand. The perspective of a patient experience of antibiotic resistance was also missing from this study. No patient advocate groups exist for this issue in New Zealand. Further work is needed to identify participants to fill these gaps in the next steps of the research. Although the sample of interviewees was weighed towards some aspects of the sampling frame, this was justified by the number of different types of roles within that particular box, or by a lack of suitable participants in other areas.

It is also worth considering that the One Health/EcoHealth basis of the model relies on there being a demonstrated transmission of AMR between animals, the environment, and humans. Although many interviewees and much of the AMR literature take this One Health concept as a given, there are also some areas of contestation, especially regarding the links between food animals and humans. This was seen in both the background

readings and in the interviews. There was consensus between the interviews and the literature that the environment is generally considered to be likely to be important for AMR, but this was a relatively under-studied and less discussed area. Overall the strength of the evidence seems to point to transmission between all three domains being possible, but the relative importance of each is less clear. Consolidating the evidence base around this and building consensus among stakeholders and policymakers will be crucial.

The simplicity of causal loop diagrams, while having some benefits acknowledged above, can potentially result in incorrect interpretations (196). Causal loop diagrams do not distinguish between information links and rate-to-level links, which can result in the situation where *"the traditional definitions of positive and negative links fail in a wide variety of cases"* (196 p. 160). That is, the presumption that a positive sign indicates variables moving in the same direction and minus sign indicates variables moving in the opposite direction may not always be applied correctly. Richardson (1986) suggests this definition of a positive influence in a CLD: *"A has a positive influence on B if an increase (decrease) in A results in a value of B which is greater (less) than it would have been had A not changed"* (p161). Future work on this model will ensure that postulated causal links are in keeping with this more robust definition. Conversion of the CLDs into quantitative models would also help eliminate this problem.

In addition, the reference mode and the CLDs currently reflect only the knowledge of participants (although these stakeholders do represent much of New Zealand's AMR expertise), and a small amount of input from the literature. The model needs to be validated more thoroughly by: testing the model with the participants themselves; triangulation with the wider AMR literature; and simulation modelling, which will allow the testing of the causal theory against real world data and trends.

It is worth noting that the loop structures are likely to change when the model is quantified in the future. Part of this will be due to changing the model format to represent stock and flow structure, which is not possible in the CLDs. This may require some explanation to stakeholders, as the loops may seem to no longer align directly with their cognitive maps. However, such changes are a normal part of the iterative process of model building.

The size and complexity of my model may be another limitation. Ghaffarzadegan *et al.* (2011) make a case for the usefulness of small system dynamics models in the public policy process. They suggest that the optimal model size is a few significant stocks and a maximum of seven or eight major feedback loops (156), in order to allow capturing of key insights while maintaining ease of understanding and communication of the issues. By these criteria, the overall model resulting from my research may be too large to aid policy making at this stage. However, the separate CLDs fit within the optimal size suggested by Ghaffarzadegan *et al.* (2011). Further work could address this issue by simplifying the overall model further.

8.4 Implications for policy and future research

This study indicates that addressing AMR will require consideration of intertwined issues such as poverty and inequity, farming practices, water quality, widespread use of chemicals, impacts of globalisation, and the 'for-profit' model of medicine development. This research suggests that an ongoing lack of consensus between various experts on AMR is likely to hinder effective policy-making. While diverse viewpoints are legitimate and contribute meaning, and there may be no 'one truth' about AMR, further work to foster collaboration and understanding between disciplines will be beneficial. Many participants highlighted the need for such an approach. Greater understanding of alternate perspectives may increase trust and reduce blame by ensuring all parties feel heard. The participatory system dynamics model developed in this study helps by bringing diverse understandings together into a shared causal theory of the system.

The large number of reinforcing loops identified could be interpreted as highlighting the difficulties that may be encountered as policies to reduce AMR are tried. With further work it is possible that some of these may be identified as key leverage points to target and avoid policy resistance. In order for this model to be applicable to policy and practice beyond speculation, the next steps in the participatory system dynamics modelling process (as shown in Figure 5.2) need to be carried out. However, based on these qualitative results, I make some tentative initial policy recommendations here. Several of these are structural level recommendations, which contrast with the current focus of AMR policy which tends to be on the behaviour of individual patients, prescribers and farmers.

1. There is an urgent need to improve integrated surveillance of AMR in humans, animals and the environment in New Zealand, to establish a clearer baseline understanding of the nature of the problem and the shape of change in AMR over time. This will be critical to understanding the combination of feedback processes driving AMR trends, and therefore for designing effective policy interventions.

2. Policies to improve equity in income, housing and access to primary healthcare are likely to have beneficial effects on levels of infection, antibiotic prescribing and use behaviours, and AMR. Of course, such policies will also have many other co-benefits outside of addressing antimicrobial resistance.

3. Continue to foster collaboration between different disciplines as part of a One Health approach. There were several interlinked feedback loops synthesised on this topic. These feedbacks suggest a need to find balance in terms of participation – participation needs to be broad and inclusive, whilst operationalised in a way that makes people feel progress is being made at a reasonable pace.

4. Explore alternative modes of funding for antibiotic development, as private for-profit models appear to be ineffective in this case.

5. Further develop the evidence base for non-antibiotic chemicals, including agrichemicals and personal care and cleaning products, in accelerating resistance evolution. Where evidence for these links exist (e.g. for the herbicide glyphosate (197-199)), we should take precautionary action to restrict use of these substances. Herbicides such as glyphosate have also come under scrutiny for other negative human and environmental health impacts (200).

6. Many interviewees agreed that there is a need to improve New Zealand's water quality. This might be done partly through considering farming practices and livestock numbers. Actions in this area would also have other health and environmental co-benefits.

My aim was to construct CLDs specifically for New Zealand, but it is possible that the generalised nature of many of the feedbacks means they may be applicable to other countries. However, it is likely that the relative strength of the feedbacks would vary.

This study raises a number of recommendations for future research. Further work is planned to progress the model built in this thesis. An initial step would include more in-depth triangulation with the wider AMR literature, to confirm that the postulated links in the model are supported by evidence. Another important step would involve workshops with groups of stakeholders - ideally those initially involved in this project, in addition to addressing the gaps in representation. This would be used to assess the level of consensus on the model, and likely result in some additions and refinements. Building confidence in the usefulness of the model is an important aspect of validating the model.

Group model building that involves stakeholders meeting in person would be beneficial for refining and improving the validity of the model, as well as building a shared sense of ownership and commitment to using the results of the modelling to achieve policy change. Eventually the refined qualitative model would need to be converted to a quantitative system dynamics model, to allow for more formal validity testing of the model and understanding of which feedbacks are dominating the AMR system in New Zealand. Development of a quantitative model would also enable simulation to test the effects of possible policy interventions.

Similar studies could be carried out in other countries to see how similar models are between different settings. In addition, the environment domain of AMR could be an area to explore further. Several participants in this study saw this as a potentially important, but under-studied, area. This could include testing for antibiotic levels and presence of resistant bacteria in different settings. More assessment of the links between antibiotic resistance in food animals and humans may also be beneficial, to help address some of the conflicting views on this topic. Many interviewees thought New Zealand's context (a developed country with a large number of farm animals) makes us well placed to conduct such research. More One Health research on antibiotic resistance is essential, and further exploration of EcoHealth approaches to this issue is certainly warranted.

8.5 Conclusions

The lack of integration of knowledge about what drives AMR currently means that there are conflicting views between important stakeholder groups about the most effective policies to address it. Despite the absence of a comprehensive evidence base, urgent policy decisions are needed to address AMR. 'Systems thinking', which takes a holistic approach to understanding complex systems and how the component parts interact, is particularly useful in informing policy decisions in such situations. This research has taken the first steps in a participatory system dynamics process to improve understanding of the AMR system in New Zealand, including human health, animal health, and environmental components, by drawing on a wide variety of stakeholder perspectives to develop a causal model.

Maintaining and enhancing the health and wellbeing of all New Zealanders will require a system-wide response to the threat of antibiotic resistant infections, in order to prevent disease caused by already existing resistant bacteria, and by preventing the rise and establishment of others. This project has contributed to a system understanding of the problem of AMR in New Zealand, using a novel approach. It provides a preliminary model to aid understanding of the complexity of relationships between human, animal and environmental health in relation to AMR in New Zealand. A large number of novel potential feedbacks were discovered through this model building process. The participatory dynamic causal theory provides a basis on which further quantitative modelling and testing work can be done, with the ultimate goal of guiding policy and action plans on AMR. Having a well-constructed model to inform policy decisions will improve the quality of those decisions and their effectiveness in limiting the impact of antimicrobial resistance.

This novel approach to addressing AMR holds potential for improving the quality of policy-making, acknowledging Einstein's famous statement that *"we can't solve problems by using the same kind of thinking we used when we created them."*

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10 Appendices

A. Literature Review Template
B. Cognitive mapping conventions and examples
C. Participant information sheet
D. Consent form
E. Semi-structured interview outline
F. Enlarged CLDs, with exogenous variables shown
G. Enlarged CLDs (without exogenous variables) – available as a separate booklet. Includes A3 version of Figure 7.15

Appendix A: Literature Review Template

Literature Review Summary Sheet for included papers

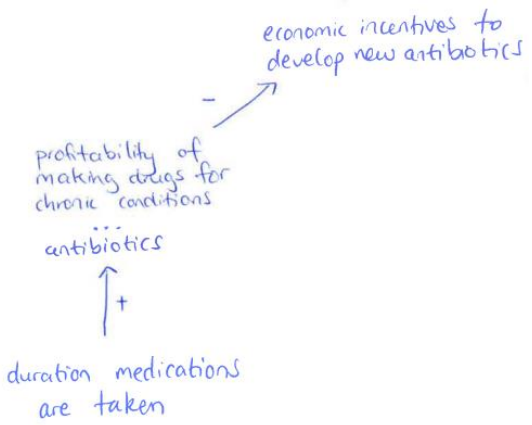
Authors:	
Title:	
Date:	
Endnote#:	

Background Methods	Key points for thesis **Dimensions covered** Human Animal Environment **Policy oriented?** **Model type**
Results	
Discussion/Conclusions	

Useful sounding references to look up:

Appendix B: Cognitive mapping conventions and examples

***Cognitive mapping conventions**:* A small example is shown below.

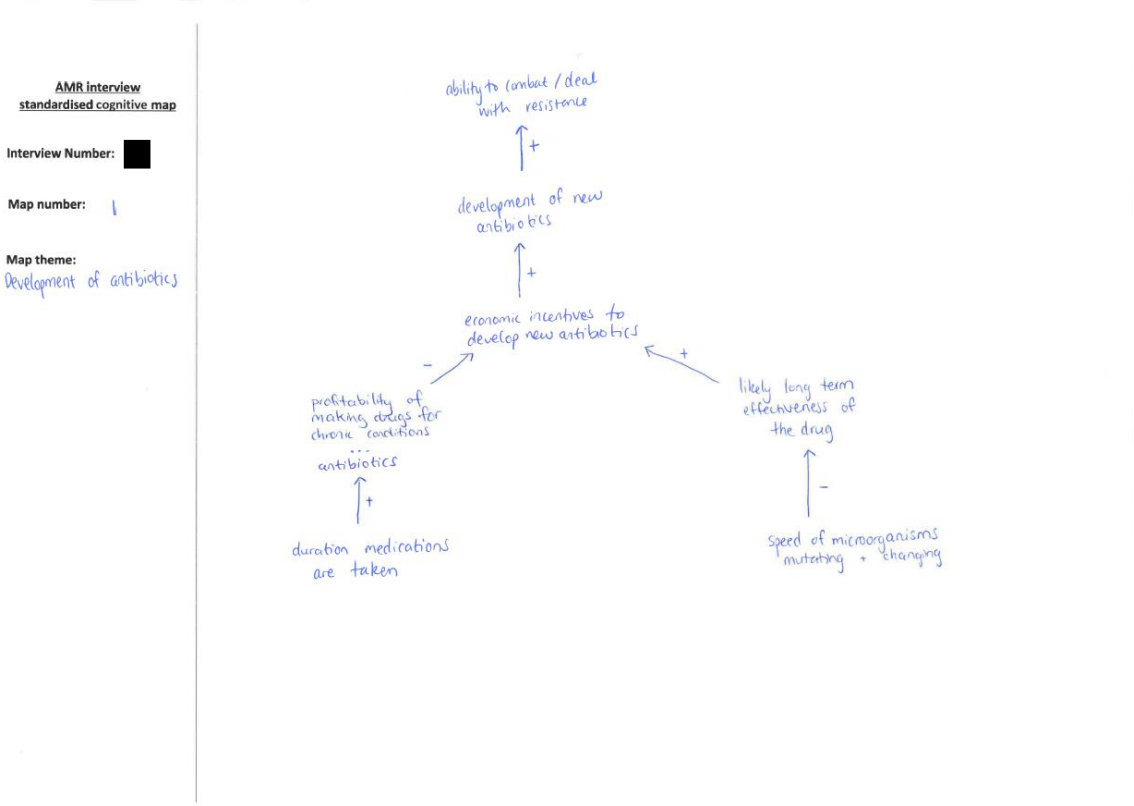


Each variable (concept/construct) is worded in such a way that it could have a 'level' – it could move up or down. For example, 'economic incentives to develop new antibiotics' is a variable that could have greater or lesser amounts. Arrows are drawn between variables to show how they are thought to be causally related. Polarities indicate the type of relationship. A "+" sign next to an arrow means that if the variable at the start of the arrow changes up or down, the variable at the end of the arrow will move in the same way (more leads to more, or less leads to less). A "-" sign indicates that if the variable at the start of the arrow moves in one direction, the variable at the end will move in the opposite direction (more leads to less, less leads to more). For example, if the causal variable goes up, the dependent variable will go down. Some variables are set up as opposing poles, separated by an ellipse. The "..." is read as "rather than". For example, the profitability of making drugs for chronic conditions "rather than" antibiotics. Delay marks (II) on arrows indicate a time delay between the causal and dependent variable.

For the example above, 'duration medications are taken' is a variable written in such a way that it could go up or down. If it is a long term medication (for chronic conditions), it is likely to be more profitable for the pharmaceutical company (plus sign, same direction) compared to making antibiotics which are short term medications. If the profitability of making drugs for chronic conditions is higher than for antibiotics, then there are less economic incentives to develop new antibiotics (minus sign, opposite

direction). In cases where variables link in such a way to form loops, these are called feedback loops.

Cognitive map examples (all from one interview)



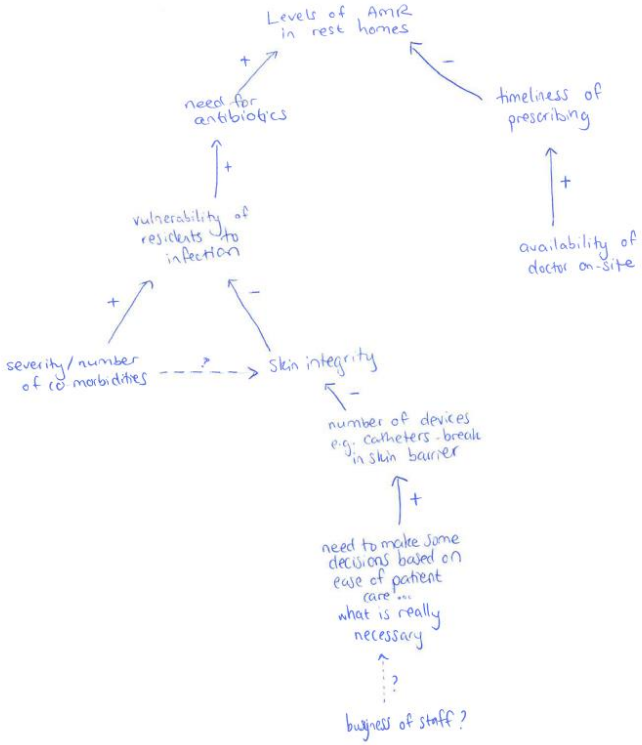
AMR interview
standardised cognitive map

Interview Number: [redacted]

Map number: 2

Map theme:

Age res. dential care



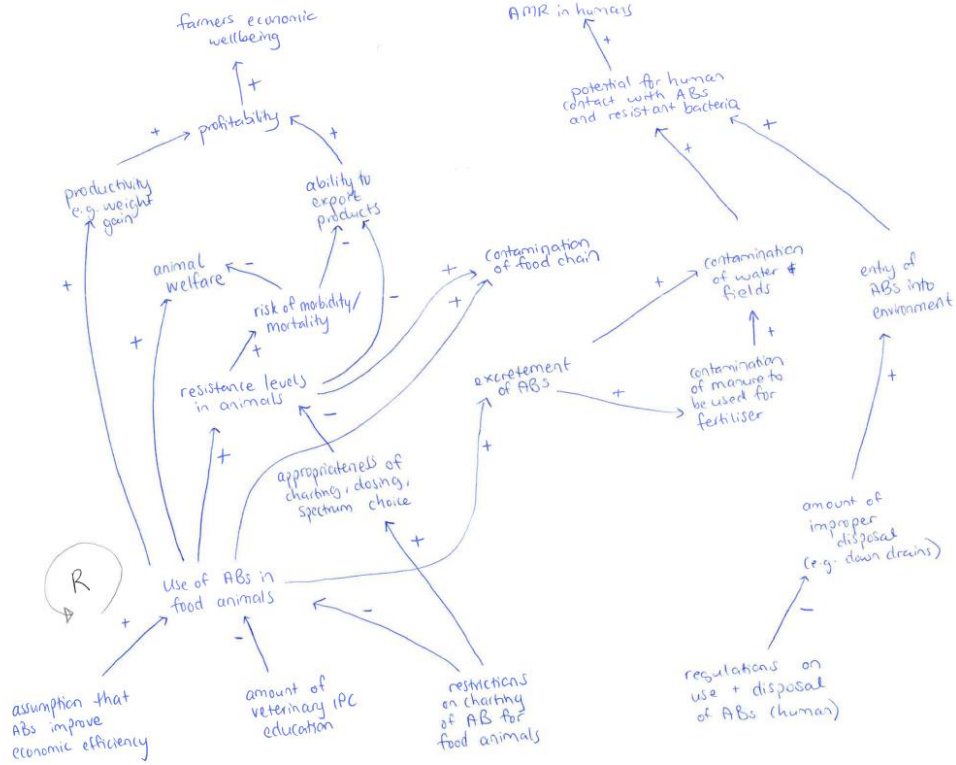
AMR interview
standardised cognitive map

Interview Number: [redacted]

Map number: 3

Map theme:

Food animals + environment



?

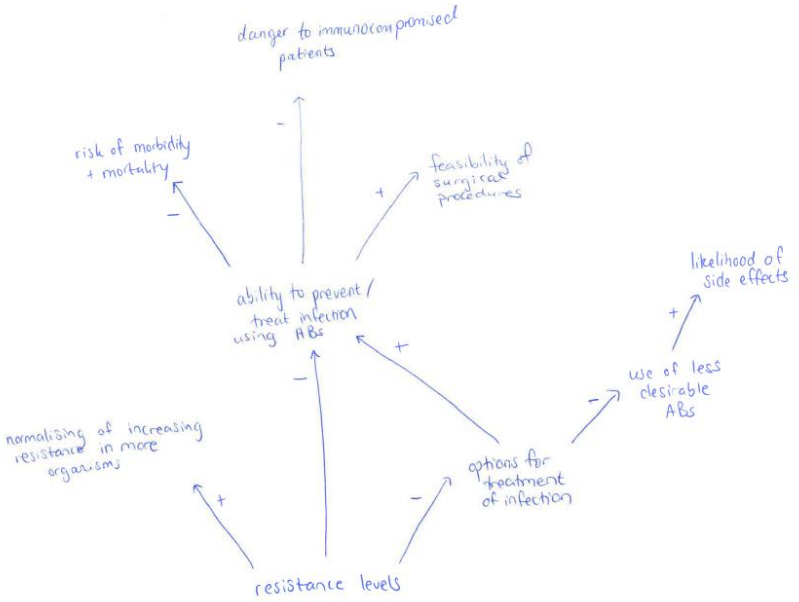
AB = antibiotic

AMR interview standardised cognitive map

Interview Number: [redacted]

Map number: 4

Map theme:
Effects of AMR in humans

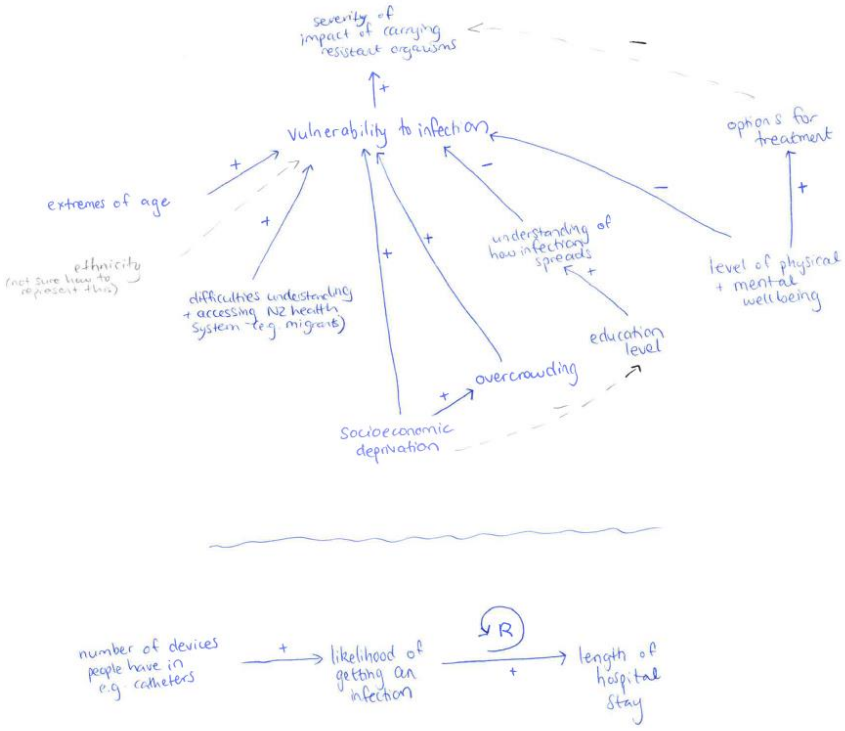


AMR interview standardised cognitive map

Interview Number: [redacted]

Map number: 5

Map theme:
Individual factors (human)



wasn't sure how to include rural vs urban

ethnicity doesn't have 'levels' - keep aside for now

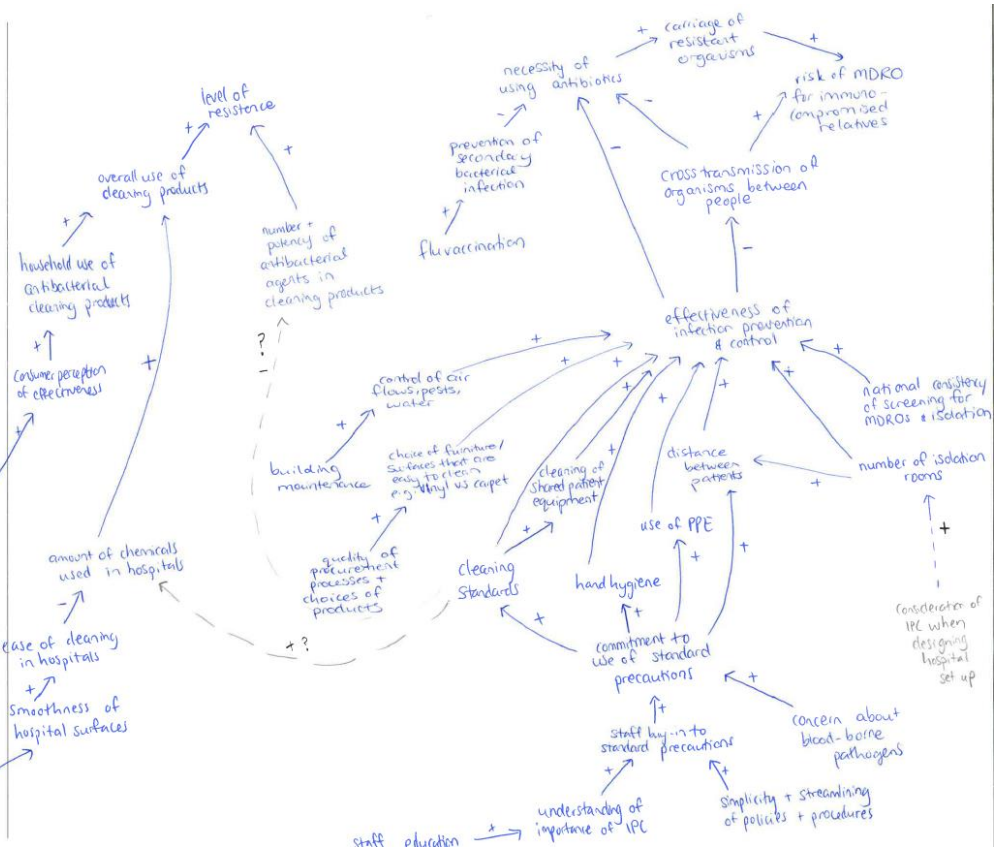
AMR interview standardised cognitive map

Interview Number: [redacted]

Map number: 6

Map theme:

Cleaning products + hospital IPC factors



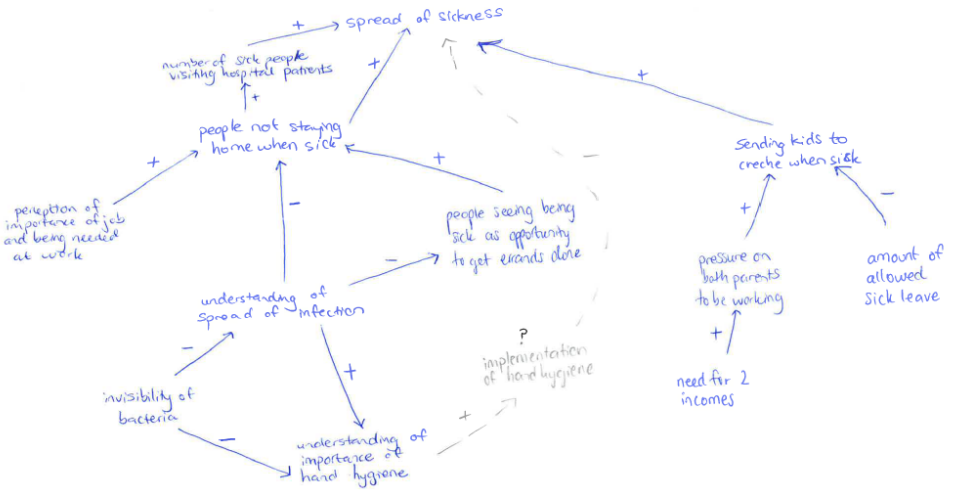
AMR interview standardised cognitive map

Interview Number: [redacted]

Map number: 7

Map theme:

People not staying home when sick



AMR interview standardised cognitive map

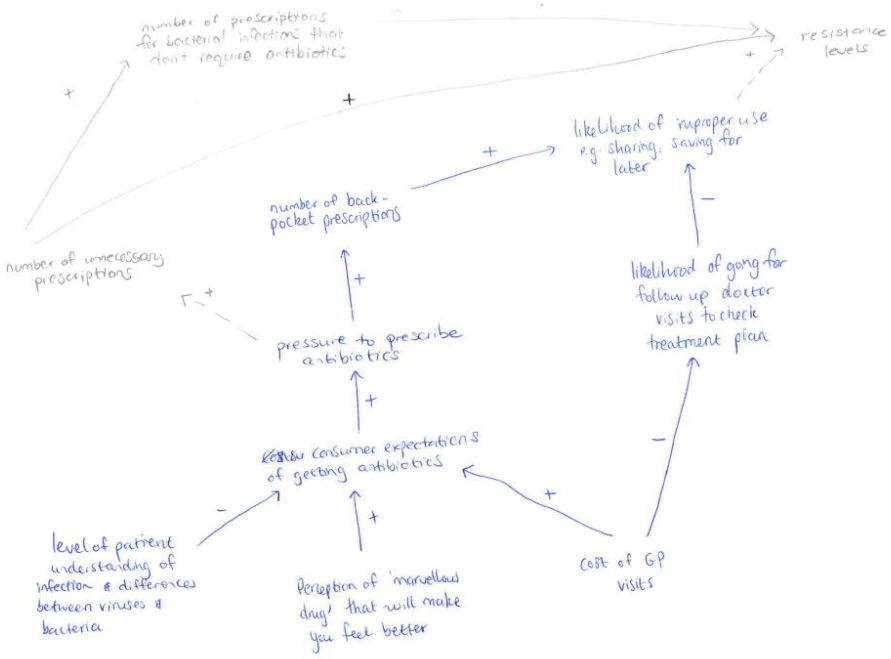
Interview Number: [redacted]

Map number: 8

Map theme:

Patient expectations

? Doctor - patient relationship - how that fits in



AMR interview standardised cognitive map

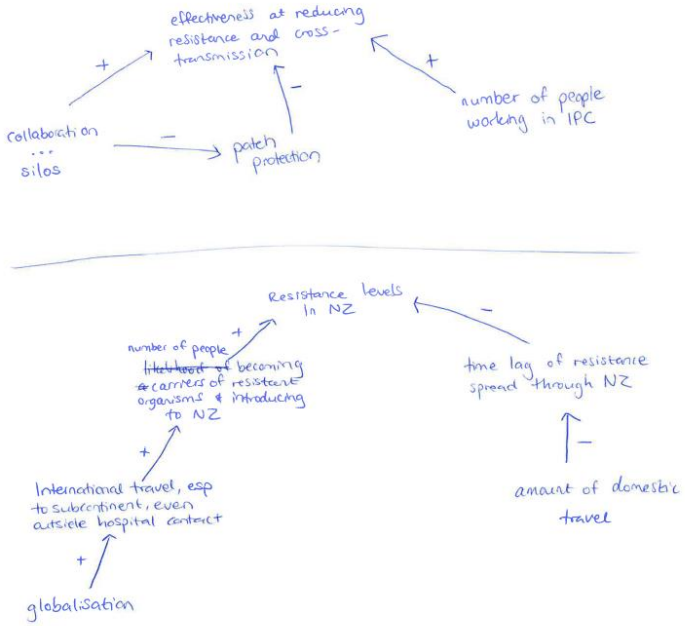
Interview Number: [redacted]

Map number: 9

Map theme:

Silos

Travel



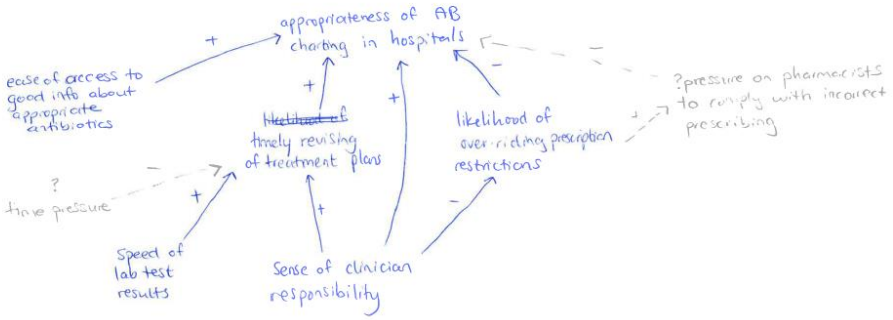
AMR interview
standardised cognitive map

Interview Number: [redacted]

Map number: 10

Map theme:

Strictness of prescribing



Appendix C: Participant information sheet

Understanding antimicrobial resistance in New Zealand

INFORMATION SHEET FOR PARTICIPANTS

Thank you for considering the request to take part in this study. Please read this information sheet carefully before deciding whether or not to participate.

This project is being undertaken for Sarah Mitchell's Master of Public Health (MPH). Antimicrobial resistance (AMR) is a growing global public health crisis that threatens our ability to effectively treat and prevent infectious diseases. We aim to bring together human, animal and environmental health perspectives about AMR in New Zealand. This will be done using systems thinking, which is a way of looking at complex problems that seeks to understand the interconnections between elements of a system. Interviews with stakeholders will be used to build up a combined picture of the system to inform AMR policy in New Zealand.

We are looking for expert stakeholders in some part of the dimensions above (human, animal and environmental health), from policy, clinical practice, science, community and industry, who are in a position to understand and/or influence policy. You have been invited to participate as you are a member of one or more of these groups.

Should you agree to take part in this project, you will be asked to take part in one interview with the research student. Sarah will travel to interview participants.

During the interview, mapping diagrams will also be drawn to picture the relationships between cause and effect during the interviews. This map will be checked with you to confirm it accurately reflects your perspective. The interview process is likely to take between 60-90 minutes. The interview will be audio-recorded and transcribed and, following the interview, your transcript and map will be provided to you so that you can check its accuracy. The stakeholder interviews will be analysed to draw out a collective understanding of AMR in New Zealand. The research student, her supervisors, and a research assistant will have access to the interview information.

The data collected will be securely stored in such a way that only the research student and her supervisors will be able to gain access to it. Data obtained as a result of the research will be retained for **5 years** in secure storage. Audio-recordings will be destroyed after interviews have been transcribed and reviewed by the participant. The

results of the project may be published and will be available in the University of Otago Library (Dunedin, New Zealand). Results of the study will also be made available to you as a stakeholder report at the end of the project.

The group of New Zealand experts in AMR is small, and maintaining anonymity in this project will be difficult. We will take care when using quotes to minimise the likelihood of attribution to individuals. You will be given the option of being acknowledged as an individual contributor, having your organisation listed as a contributor, or neither, in any written reporting.

Your participation is voluntary, and you can end the interview at any time, without any disadvantage to yourself. We will provide you with a transcript of your interview for your review and confirmation of accuracy. You can withdraw any information given up to the point of transcript confirmation.

If you have any questions about our project, either now or in the future, please feel free to contact:

Dr Alex Macmillan

Department of Preventive and Social Medicine

University Telephone Number: +64 3 479 7196

Email: alex.macmillan@otago.ac.nz

This study has been approved by the Department stated above. However, if you have any concerns about the ethical conduct of the research you may contact the University of Otago Human Ethics Committee through the Human Ethics Committee Administrator (ph +643 479 8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

Appendix D: Consent form

UNDERSTANDING ANTIMICROBIAL RESISTANCE IN NEW ZEALAND

CONSENT FORM FOR PARTICIPANTS

I have read the Information Sheet concerning this project and understand what it is about. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage.

I know that:

1. My participation in the project is entirely voluntary;

2. I am free to withdraw from the project up until the time I confirm my interview transcription, without any disadvantage;

3. Audio recordings will be destroyed after the interview has been transcribed and then reviewed by me, but any raw data on which the results of the project depend will be retained in secure storage for five years;

4. This project involves an open-questioning technique. The general line of questioning includes the causes and effects of the AMR problem and suggested policy recommendations. The precise questions have not been determined in advance, but will depend on the way the interview develops. If the line of questioning develops in such a way that I feel hesitant or uncomfortable I may decline to answer any question(s) and/or may withdraw from the project without any disadvantage of any kind.

5. I understand that it may be difficult to maintain my anonymity because of the nature of my expertise, and that any quotes used will not be attributed to individuals.

6. The results of the project may be published and will be available in the University of Otago Library (Dunedin, New Zealand) but every attempt will be made to preserve my anonymity should I wish.

I agree to take part in this project.

....

(Signature of participant) (Date)

.....

(Printed Name)

8. I, as the participant *(please tick one or two boxes as appropriate)*:

a) agree to my name being listed as a contributor in the research,	☐
b) agree to have my organisation listed in the research,	☐
c) would rather neither my name nor organisation is listed	☐

Appendix E: Semi-structured interview outline

Semi-structured Interview Sheet

Introduction

Thank you very much for agreeing to participate in this project. I am interested in finding out about your perspective on antimicrobial resistance in New Zealand. I would like to know what you think are the main problems contributing to AMR and their effects. I am interested in all aspects of AMR, including human, animal and environmental health. I will be focusing on the relationships between variables you identify in this interview and will be mapping these out as we talk. At the end of the interview I will show you this map and make sure it accurately reflects what you have told me. I will be audio recording this interview and transcribing it so I can analyse it more thoroughly. This information will help me to build up a shared picture of how stakeholders think about AMR in New Zealand. I will share the results of this project with you in a report.

Warm up

Before I get into the main questions about the causes and effects of AMR, I'd just like to ask a few more general questions about yourself and what you think about AMR.

- Could you start by telling me a bit about what your role is in your organisation and how it relates to AMR? I believe you also have roles in…
- What was it about this project that interests you/made you want to take part?

- What do you think has been happening to AMR over time? (E.g. has it been increasing in a linear way? Exponentially?)
- How do you see it progressing in the future if we continue business as usual? What would be the best case scenario if everyone got their act together?
- Going back to what you think is happening to AMR, what factors do you believe are underpinning this?

Questions	Prompts
- What do you think are the main causes of AMR in New Zealand?	- What do you think causes that/is underlying that? - What effect/consequences does that have? - How does it relate to/could it be related to…
- What are the effects of AMR in New Zealand?	- Short term and long term effects - How long does it take… - Who, what, when, how…. Actors, resources, information flow, imperatives - Who carries the cost of these effects? Does anyone benefit? - How might this affect equity?

Here is the map I've been drawing during the interview. Does this accurately reflect what you think? Are there any changes or additions you'd like to make? Can you explain this part in more detail for me?

Wrap up

Is there anything else you think I need to know?

What would be your top three policy recommendations to help reduce AMR in New Zealand?

Closing

Thank you very much for your time! Once I have transcribed this interview and tidied up this map I will email them to you for a final check and approval.

My supervisors are hoping to continue work on this AMR project beyond my Masters. This may involve some workshops with groups of stakeholders. Would you be willing to be contacted by them for further involvement in the future?

Appendix F: Enlarged CLDs, with exogenous variables shown

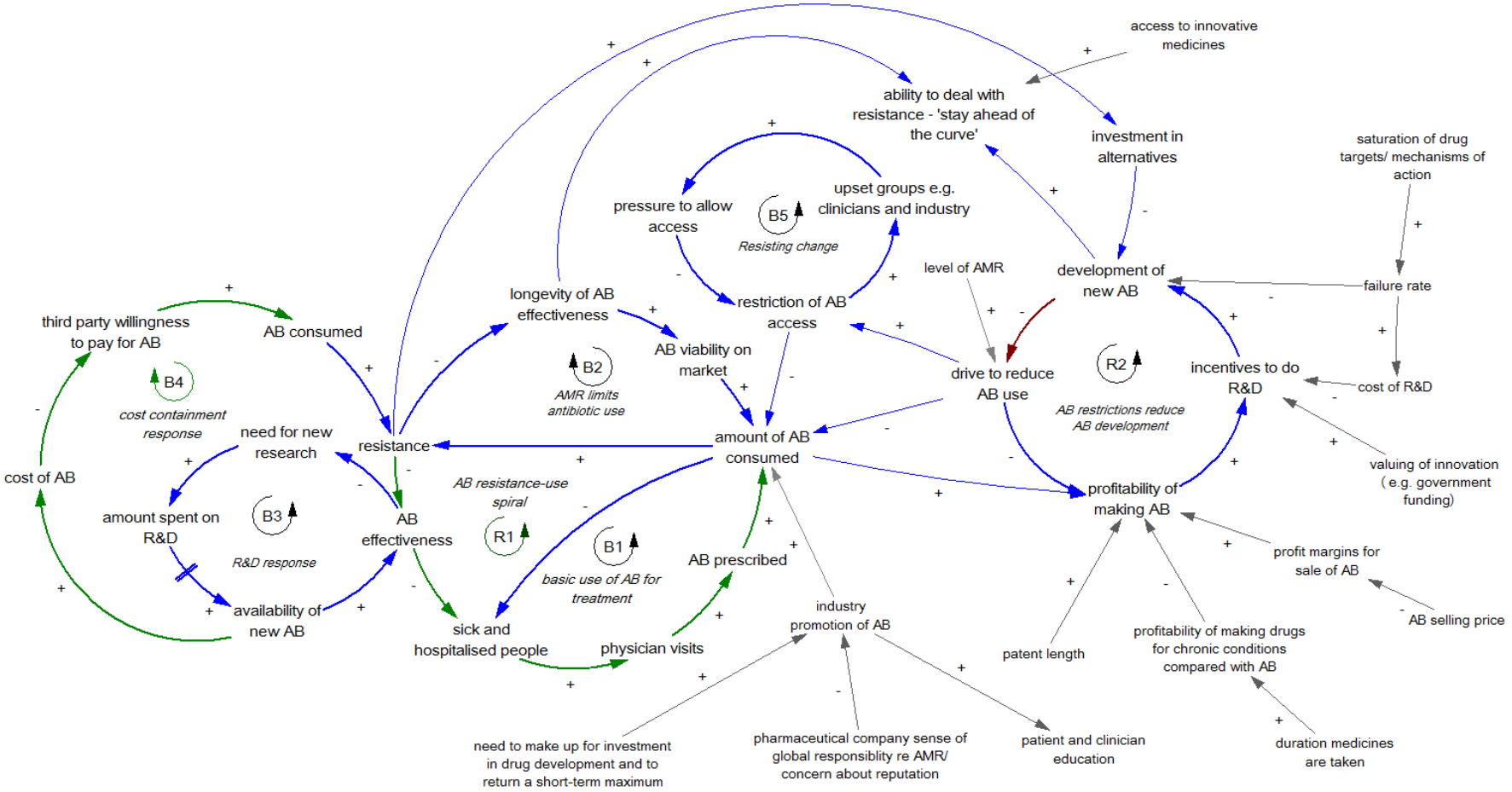


Figure F1: Enlarged version of Figure 7.2 – CLD of factors affecting development of new antibiotics (with exogenous variables)

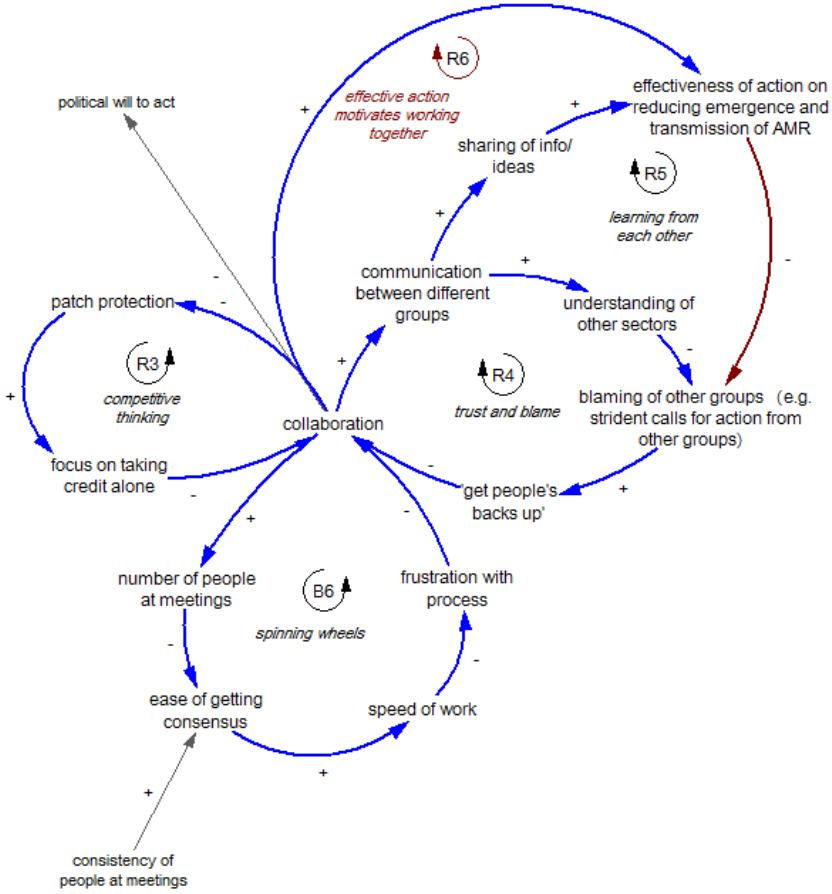


Figure F2: Enlarged version of Figure 7.3 – CLD of politics of collaboration (with exogenous variables)

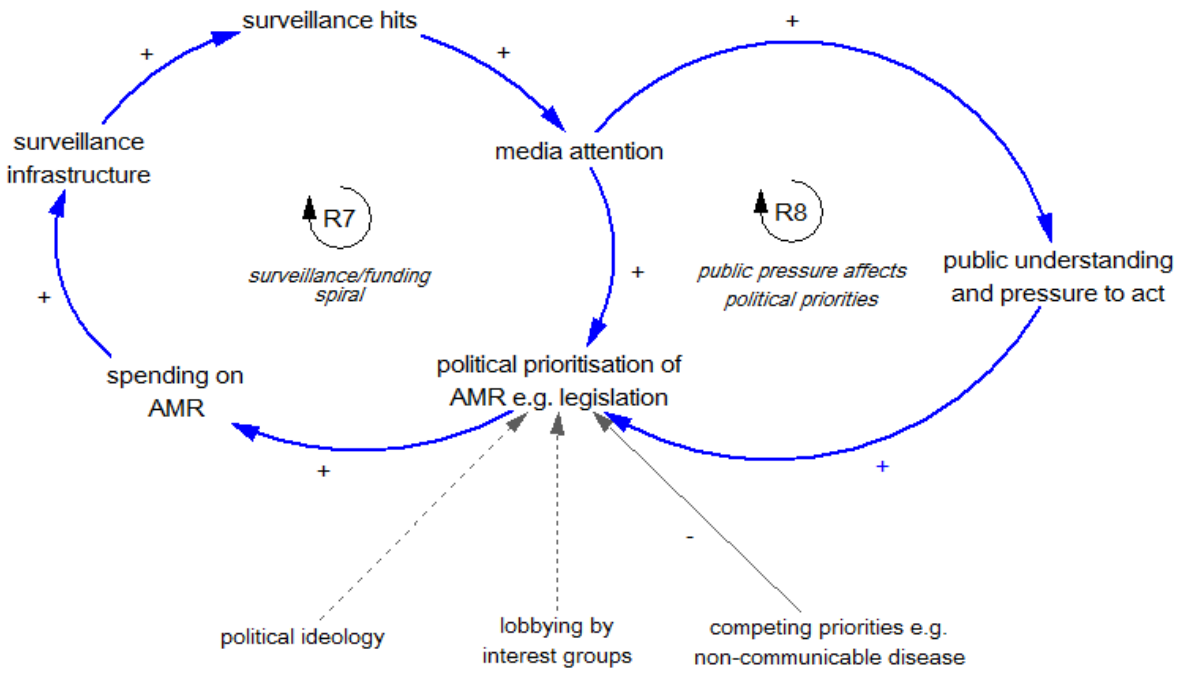


Figure F3: Enlarged version of Figure 7.4 – CLD of Political prioritisation of AMR (with exogenous variables)

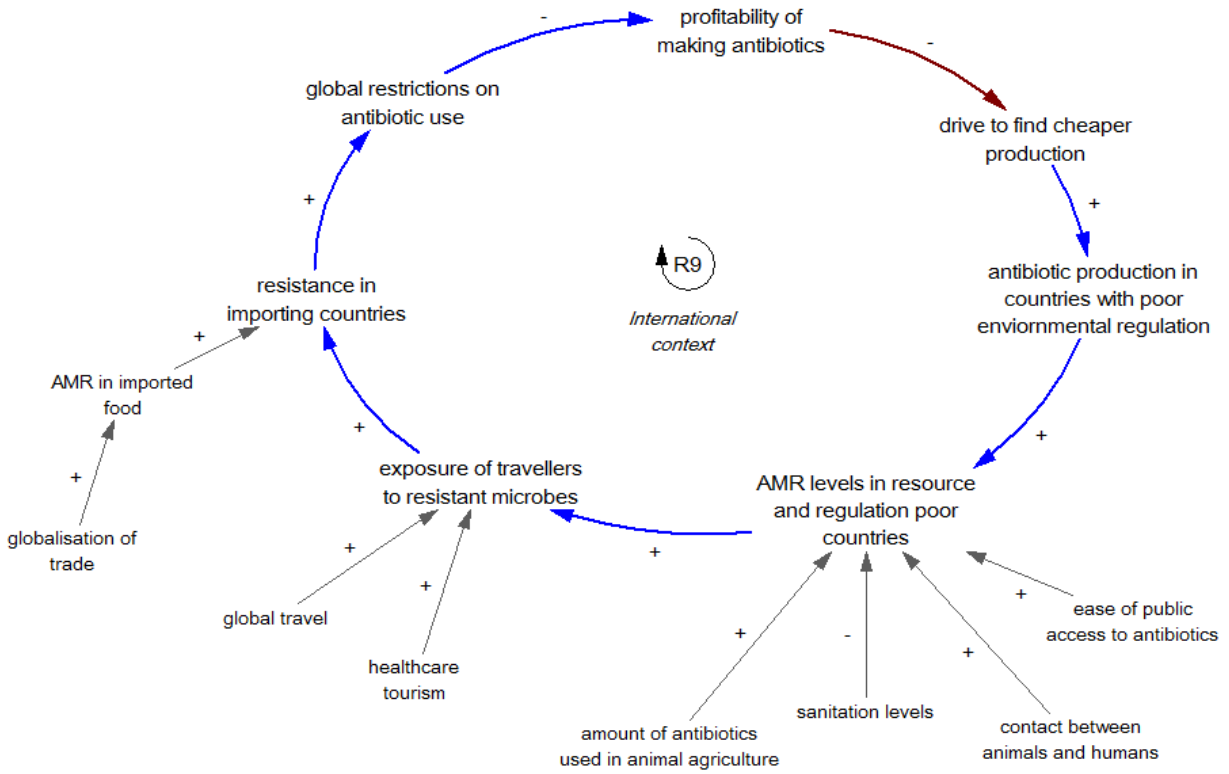


Figure F4: Enlarged version of Figure 7.5 – CLD of international influences on AMR (with exogenous variables)

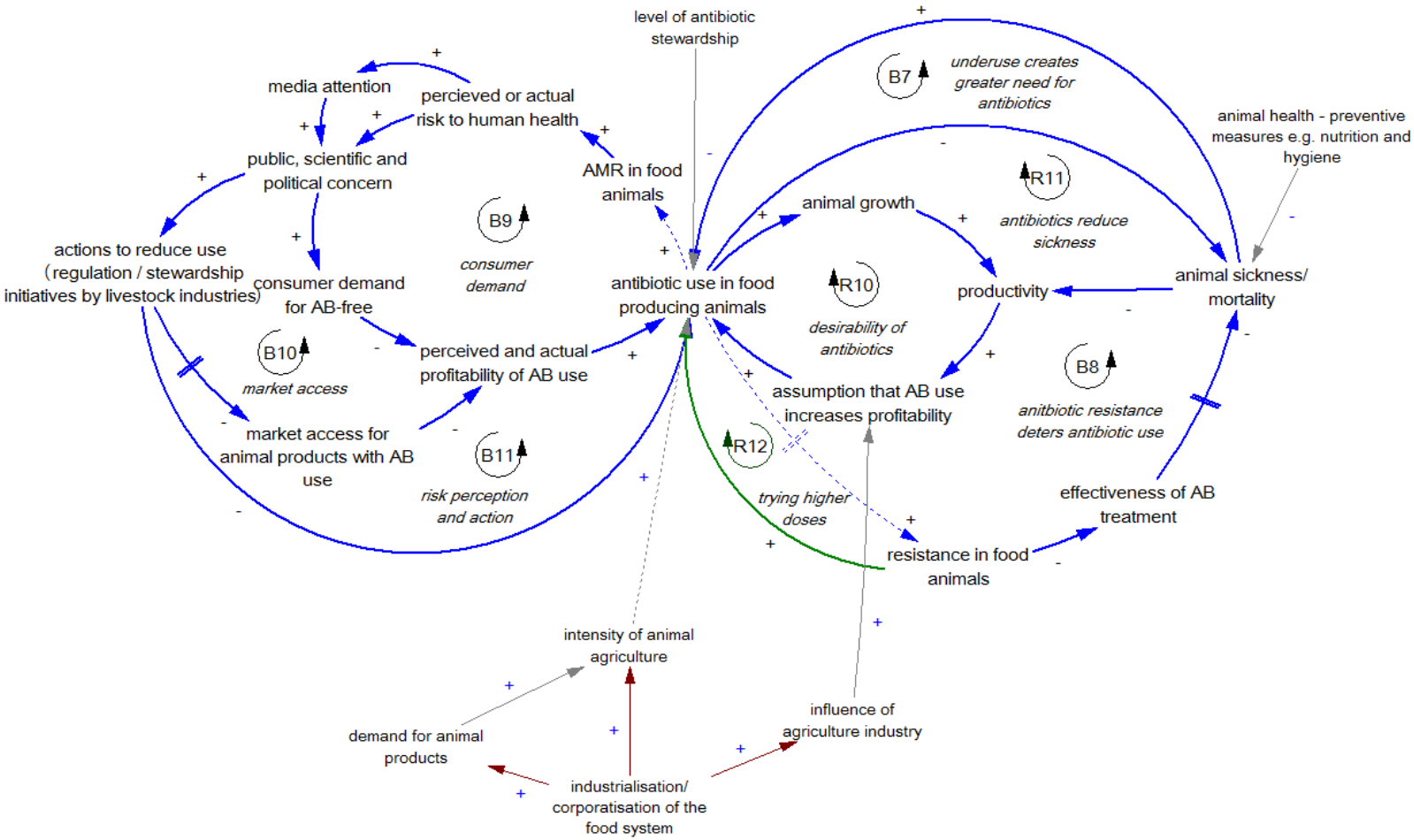


Figure F5: Enlarged version of Figure 7.6 – CLD of influences on antibiotic use in food animals (with exogenous variables)

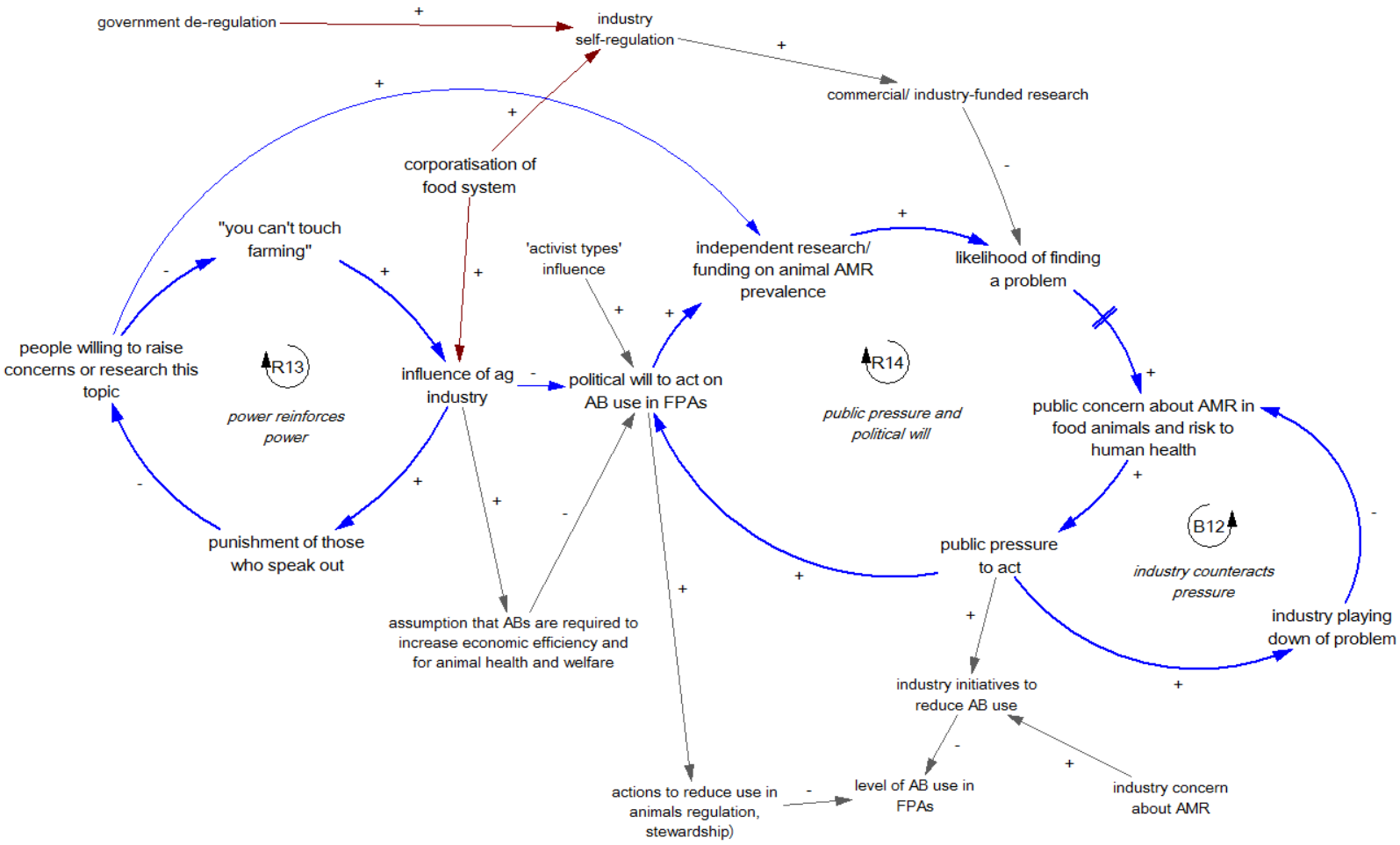


Figure F6: Enlarged version of Figure 7.7 – CLD of industry and public influences on AMR action (with exogenous variables)

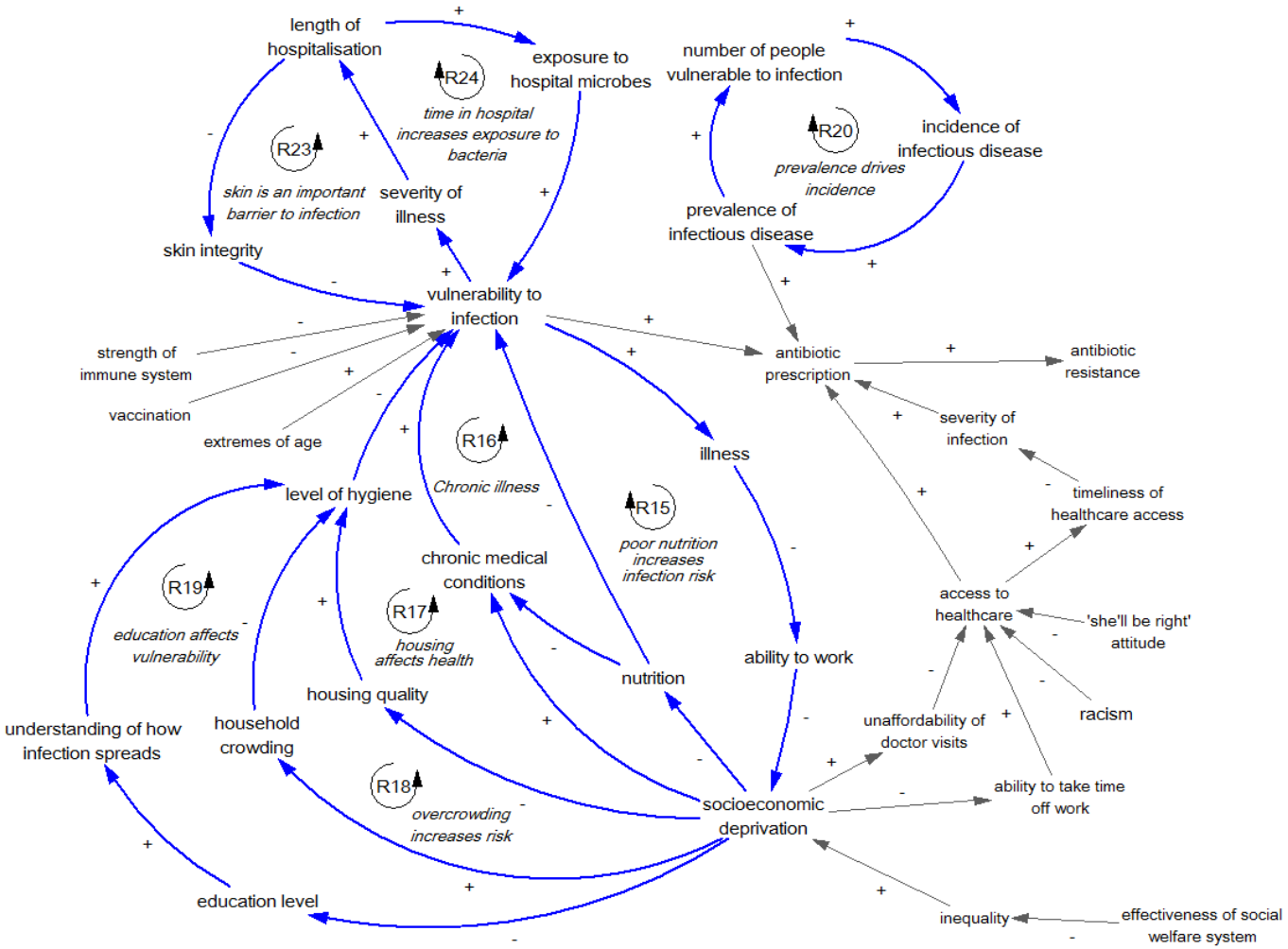


Figure F7: Combined CLDs for Figures 7.8, 7.9 and 7.11, with exogenous variables.

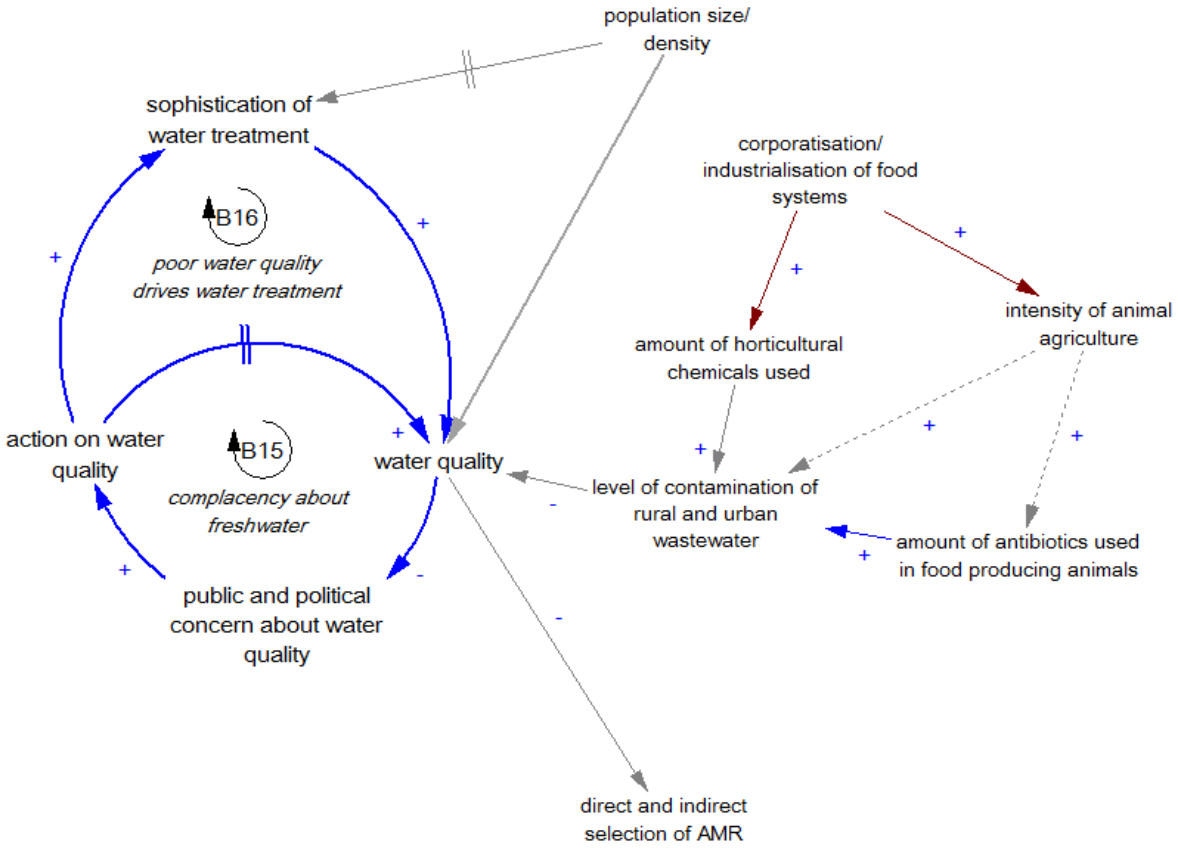


Figure F8: Enlarged version of Figure 7.7 - CLD of Water quality and AMR (with exogenous variables)

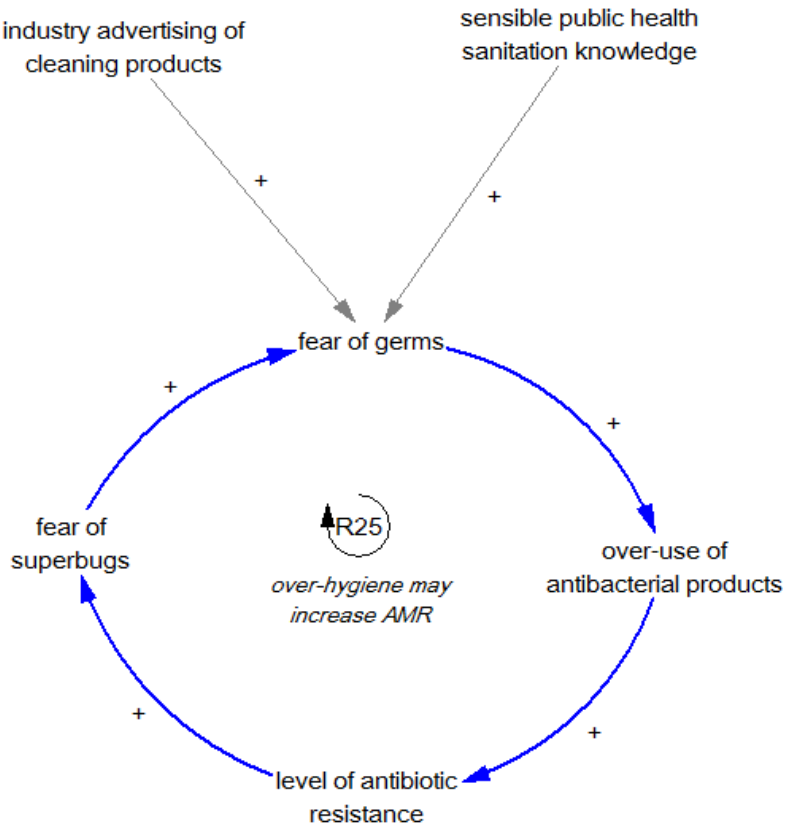


Figure F9: Enlarged version of Figure 7.8 - CLD about superbugs (with exogenous variables)

Appendix G: Enlarged CLDs (without exogenous variables)

For submission with Sarah Mitchell's Master of Public Health thesis:

An integrated approach to antimicrobial resistance in New Zealand

This Appendix provides larger versions of the causal loop diagrams in Chapter 7 of the thesis, to allow for easier viewing.

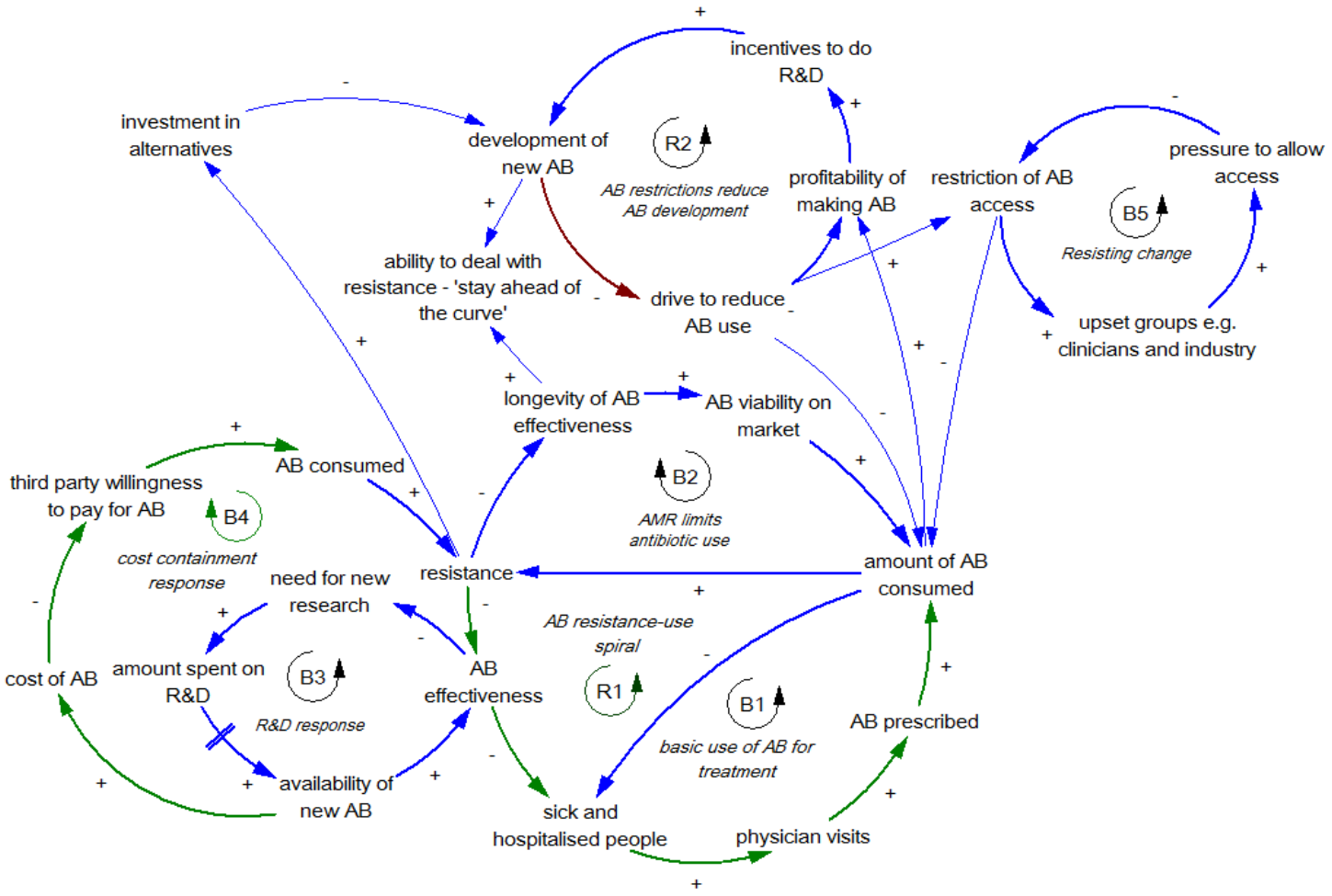


Figure 7.2 CLD: Factors affecting development of new antibiotics

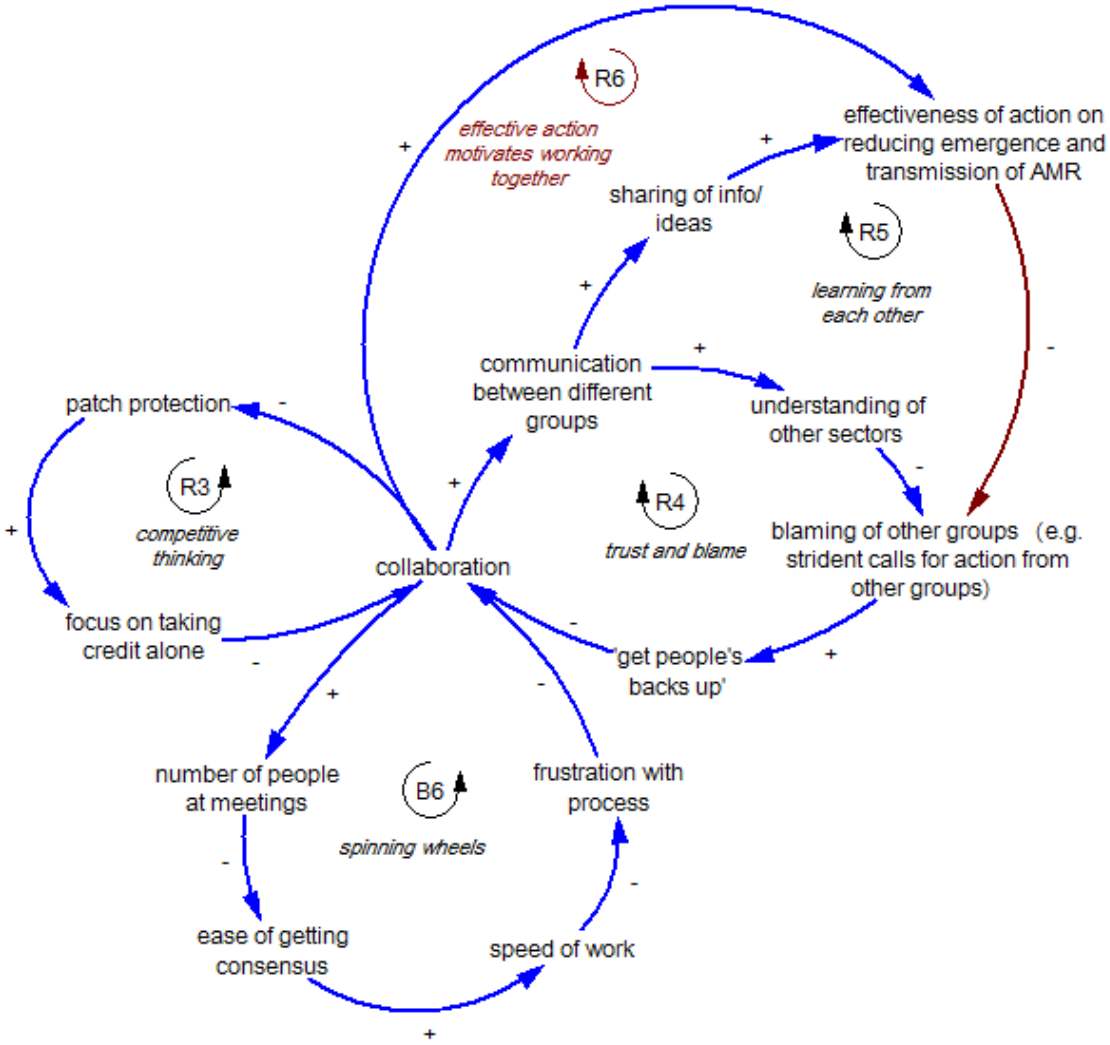


Figure 7.3 CLD: Politics of collaboration

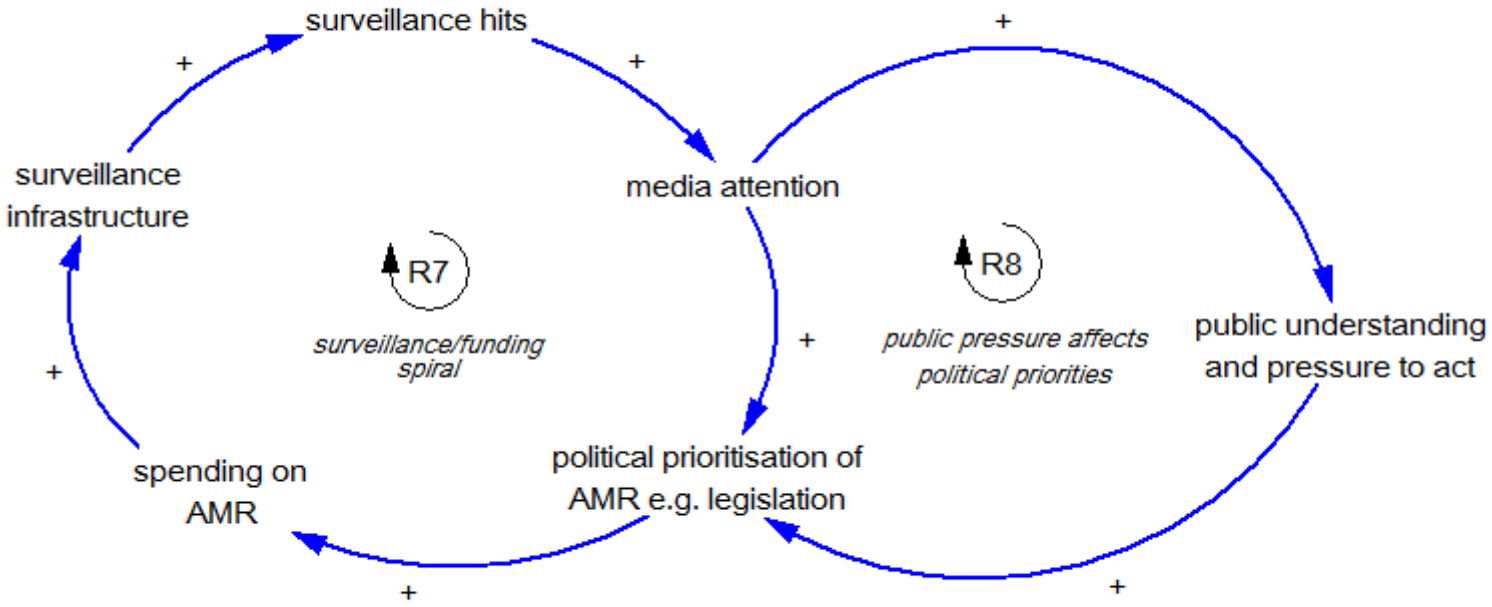


Figure 7.4 CLD: Political prioritisation of AMR

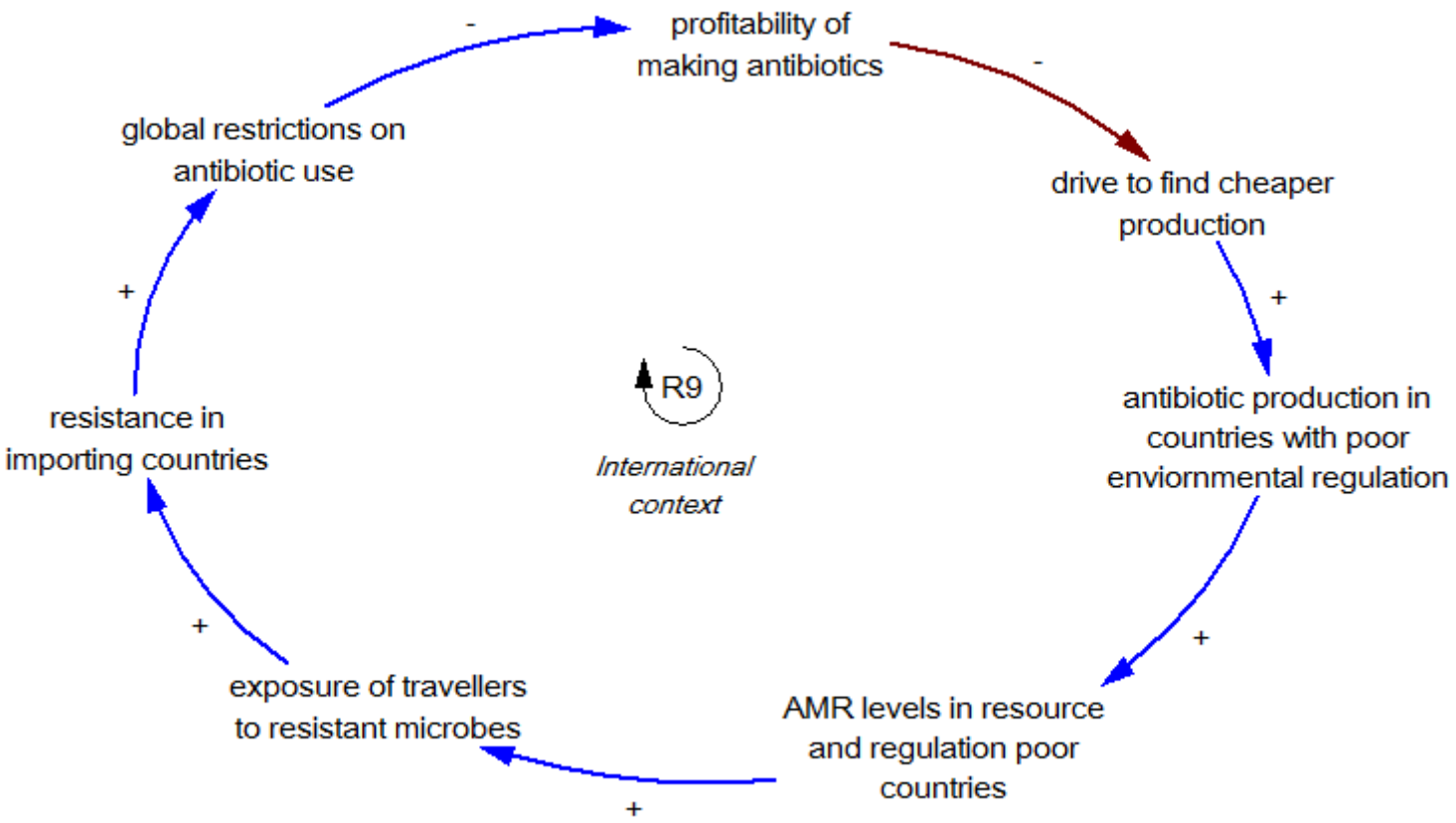


Figure 7.5 CLD: International influences on AMR

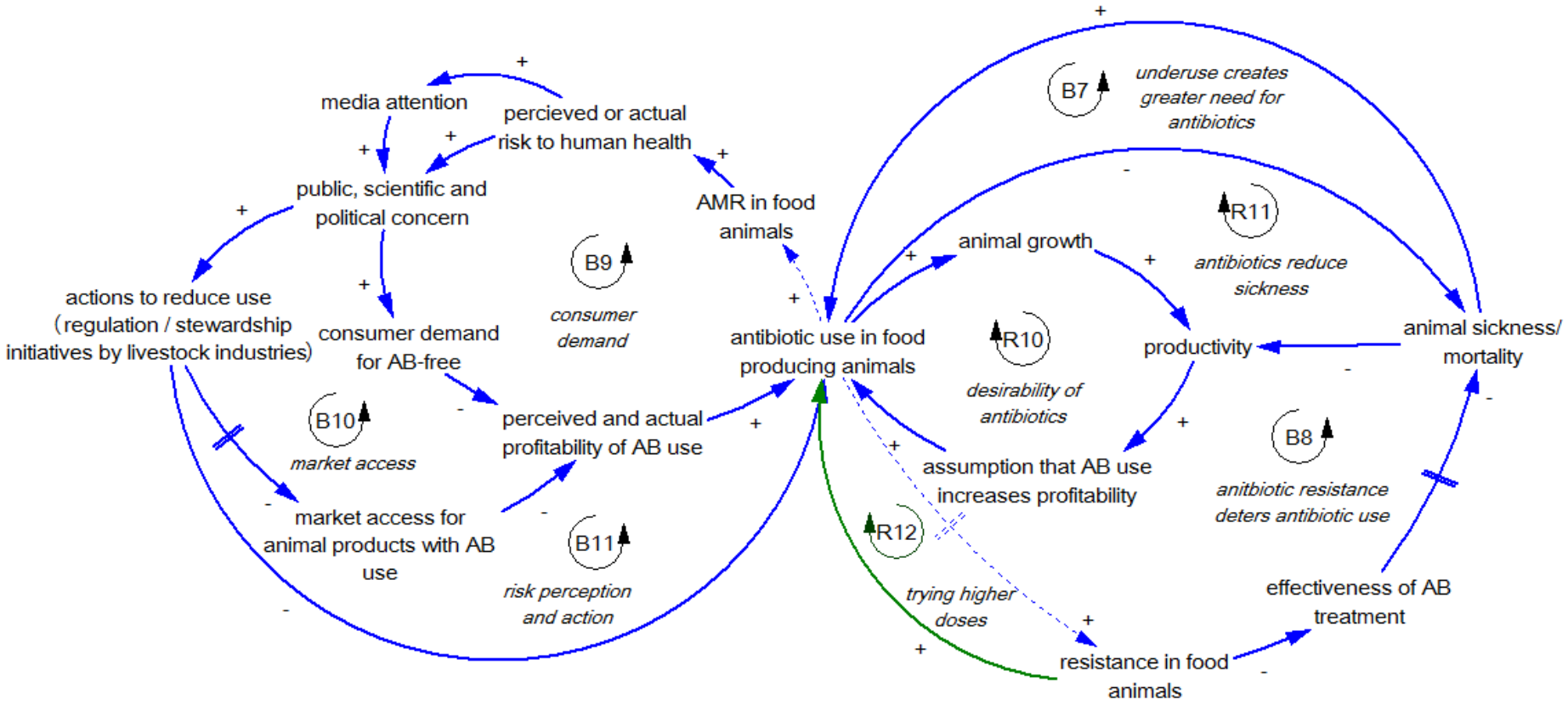


Figure 7.6 CLD: Influences on antibiotic use in food animals

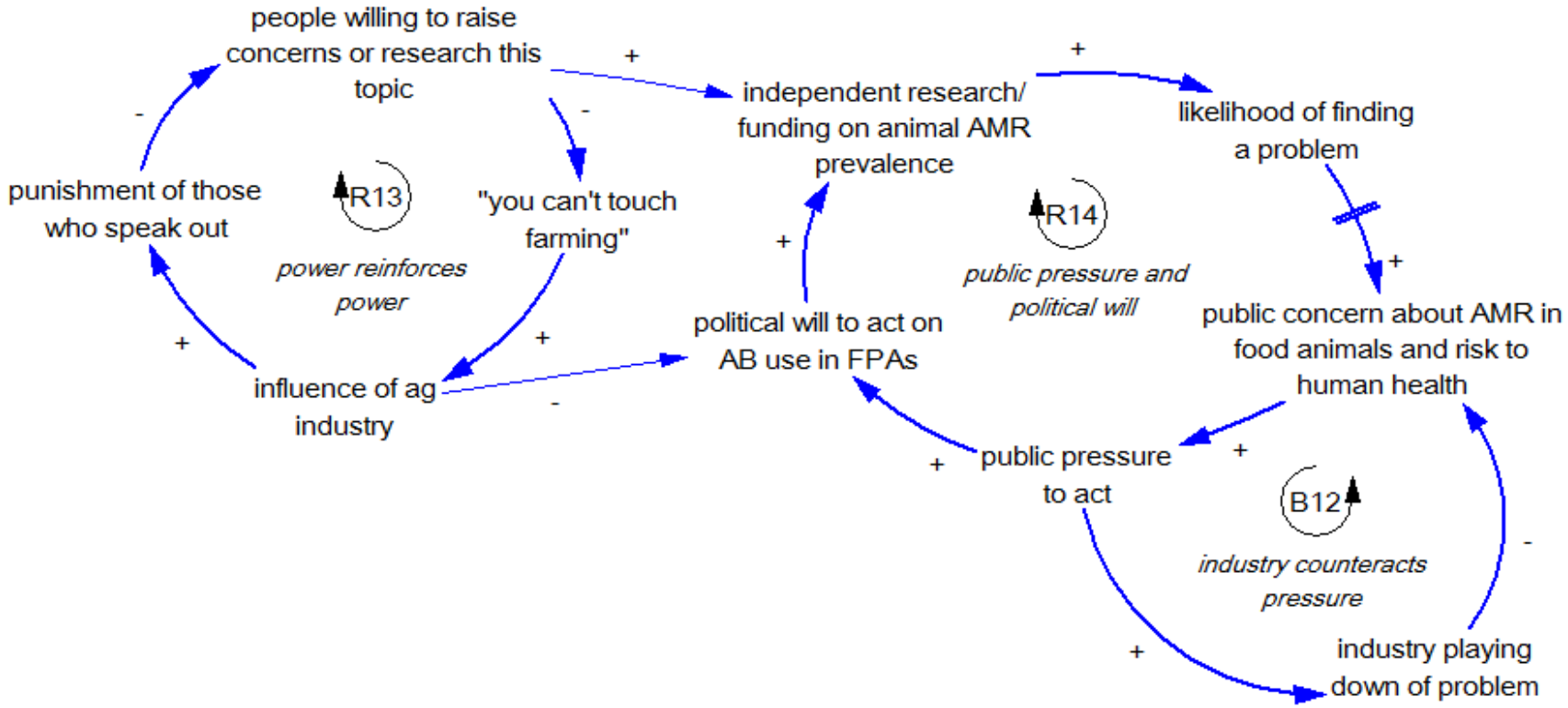


Figure 7.7 CLD: Industry and public influences on AMR action

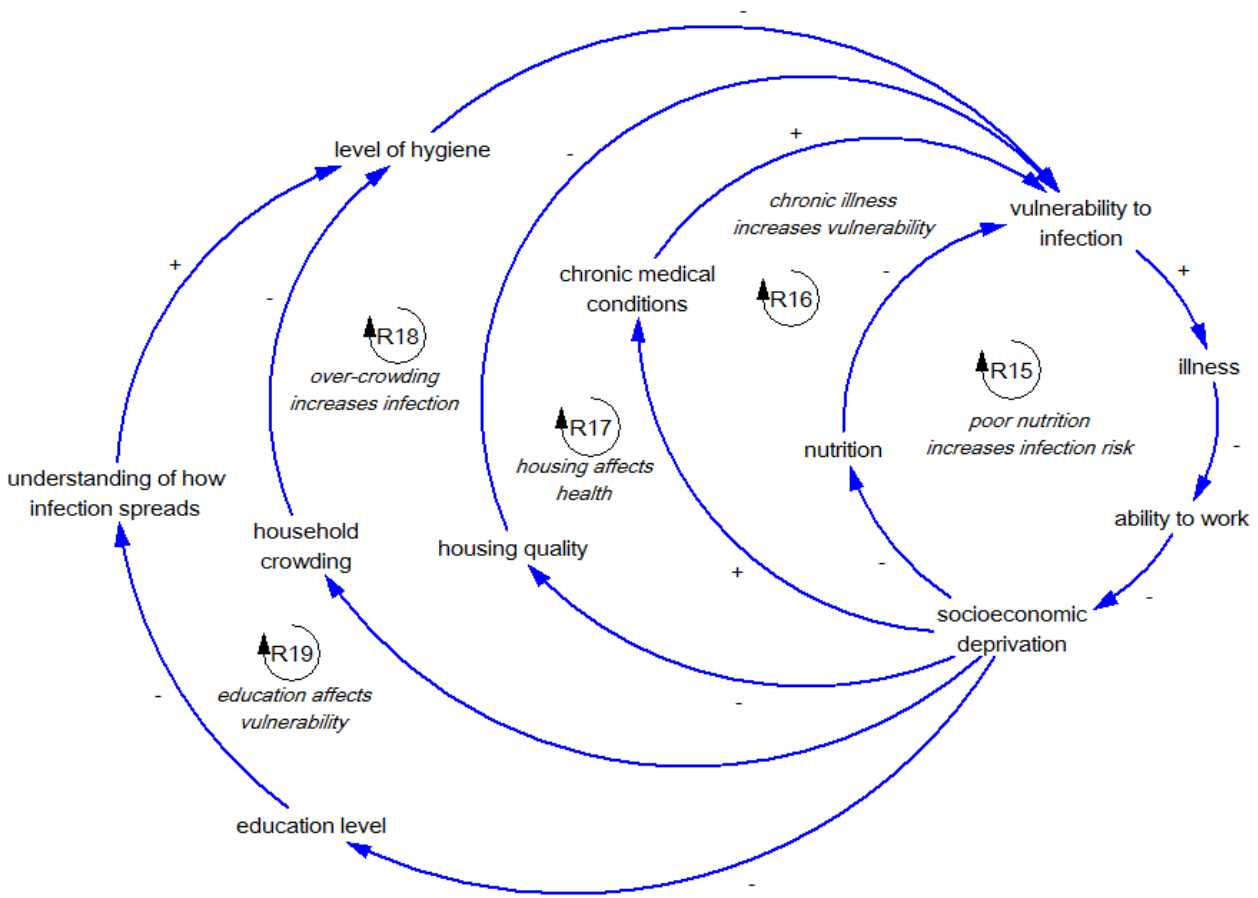


Figure 7.8 CLD: Structural inequities drive vulnerability to infection

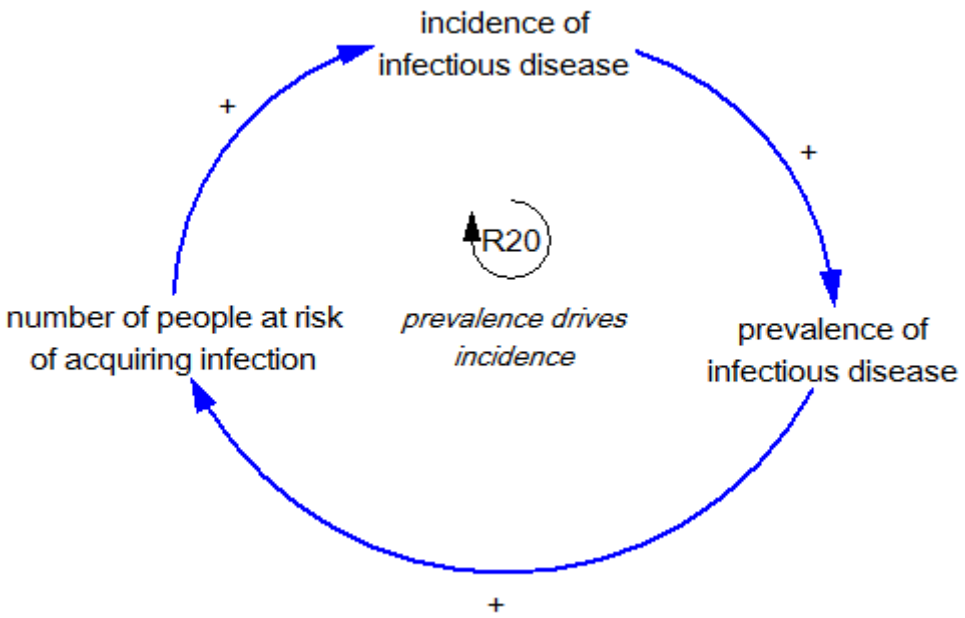


Figure 7.9 CLD: Prevalence drives incidence in the community

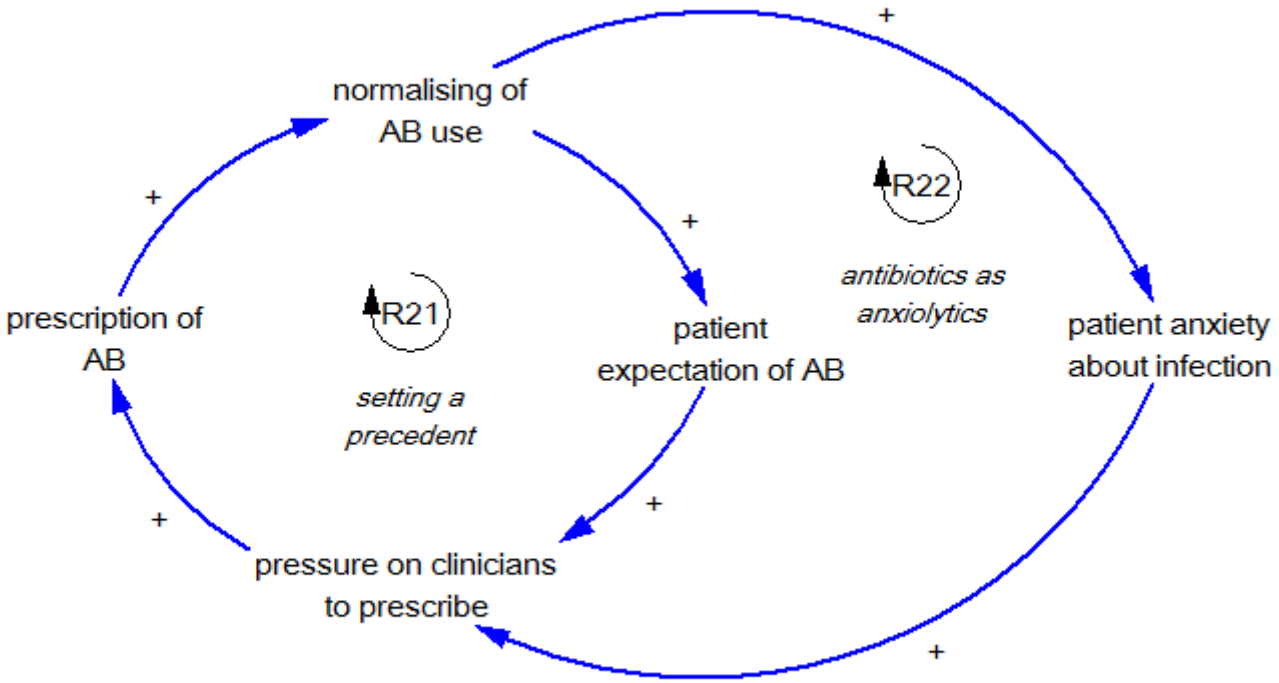


Figure 7.10 CLD: Drivers of antibiotic prescription

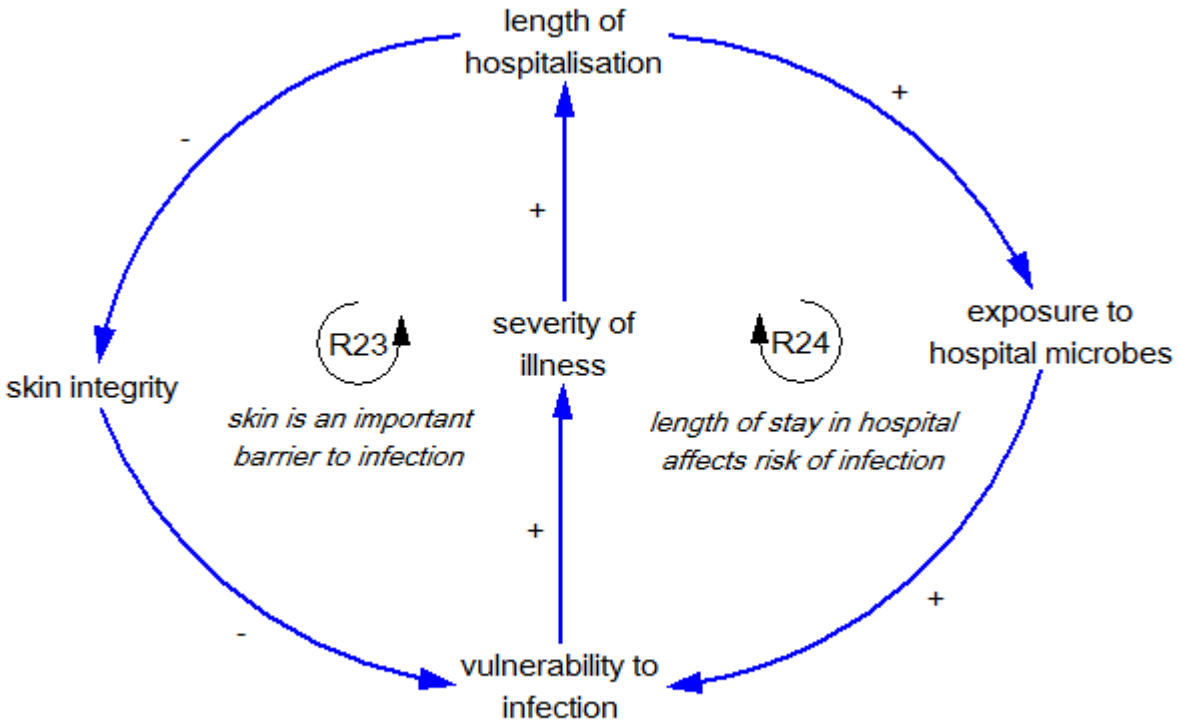


Figure 7.11 CLD: Factors increasing vulnerability to infection in the hospital context

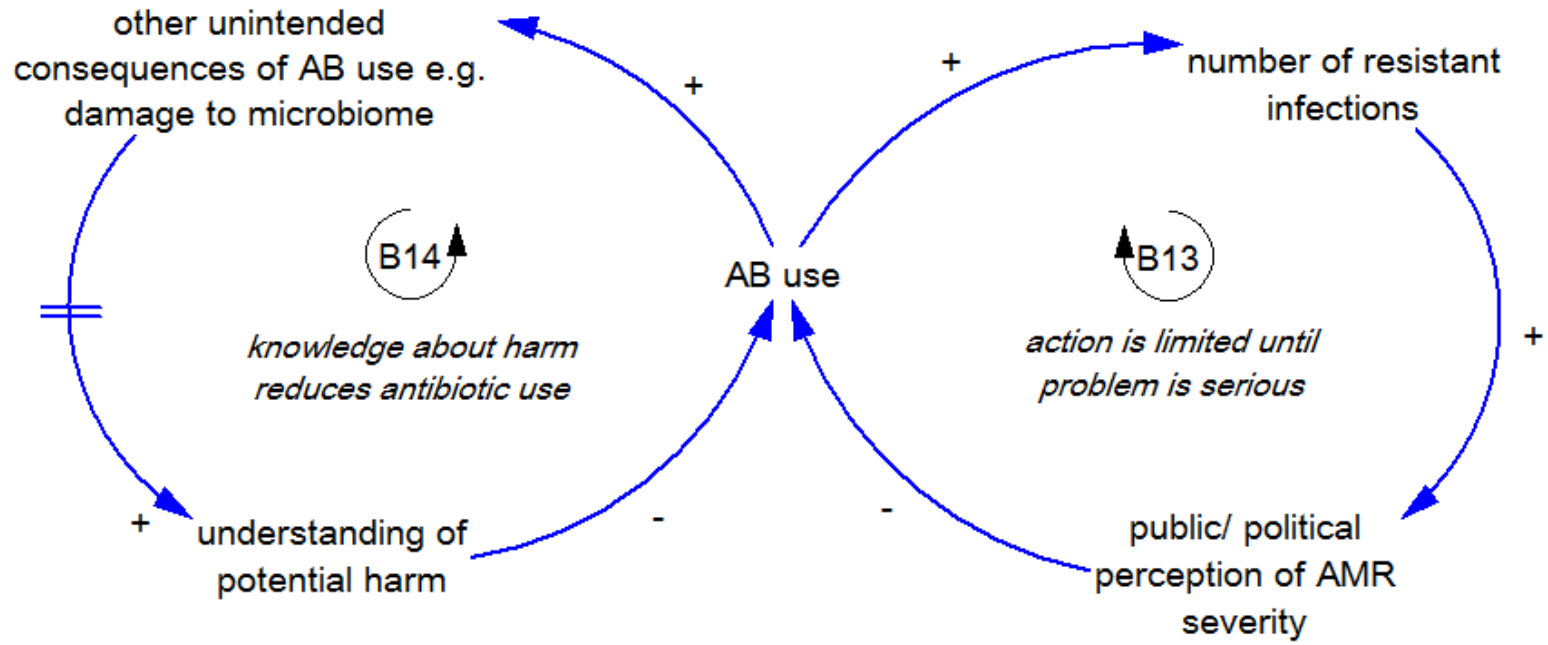


Figure 7.12 CLD: Unintended effects of antibiotic use leads to action

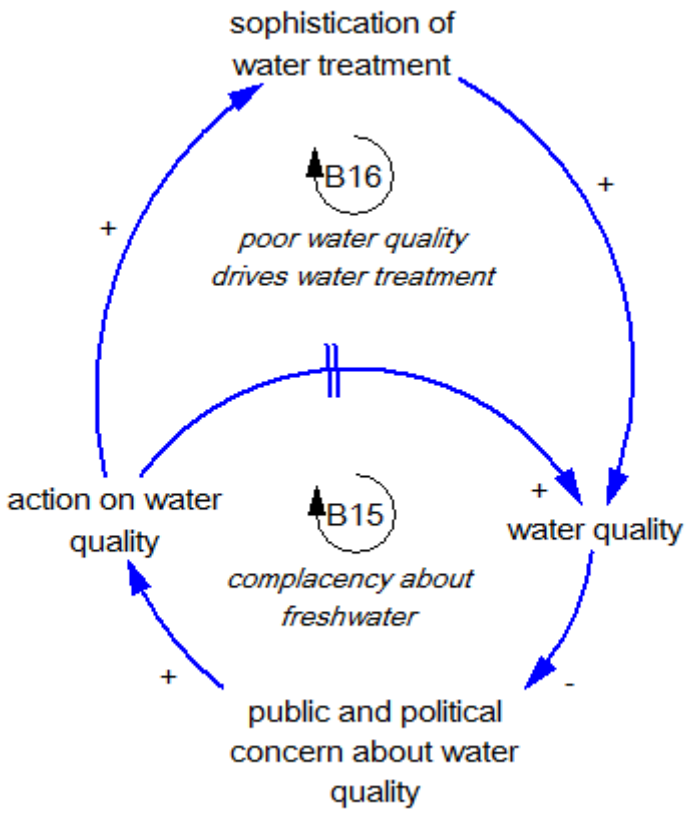


Figure 7.13 CLD: Water quality and AMR

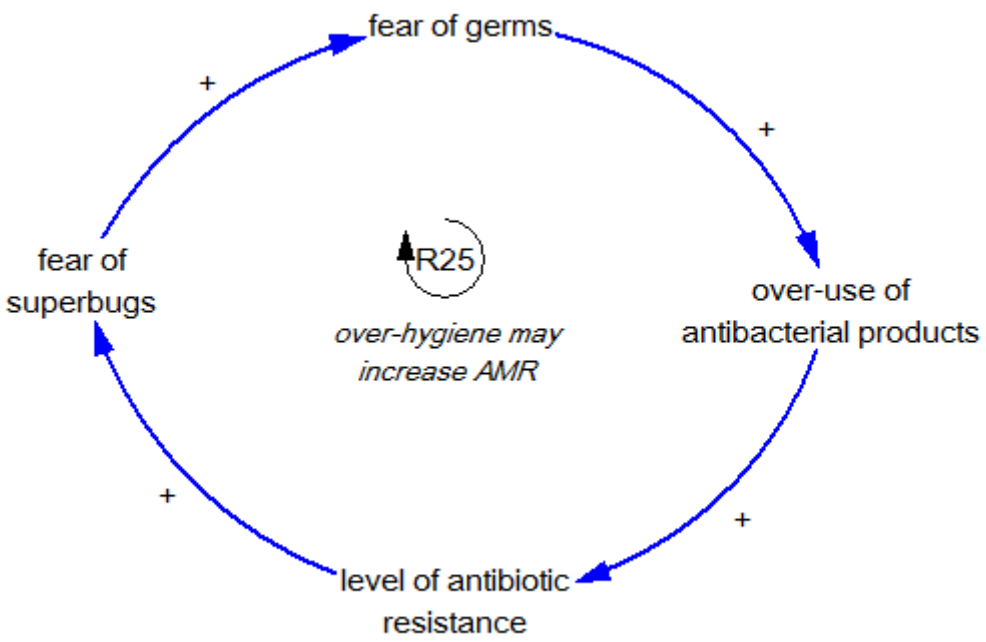


Figure 7.14 CLD: Superbugs

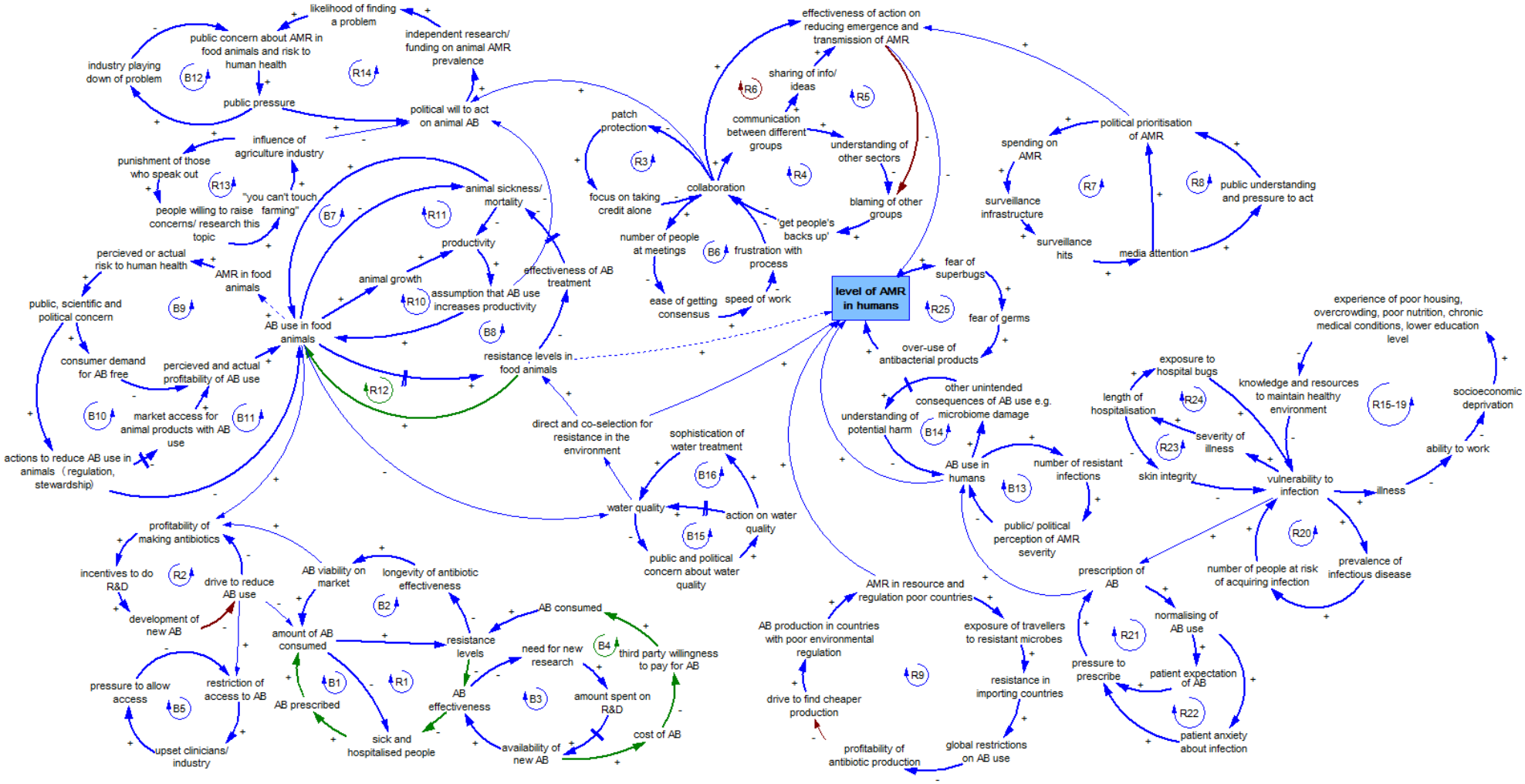


Figure 7.15 Overall model